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Induction of antigen-specific tumor immunity by genetic and cellular vaccines against MAGE: enhanced tumor protection by coexpression of granulocyte-macrophage colony-stimulating factor and B7-1. Bueler H; Mulligan RC
Howard Hughes Medical Institute, Children's Hospital, Boston, Massachusetts, USA.
Mol Med (UNITED STATES) Sep 1996, 2 (5) p545-55, ISSN 1076-1551 Journal Code: CG3
Contract/Grant No.: CA63399, CA, NCI

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Document type: JOURNAL ARTICLE

BACKGROUND: A number of tumors express antigens that are recognized by specific cytotoxic T cells. The normal host immune responses, however, are not usually sufficient to cause tumor rejection. Using appropriate immunization strategies, tumor-specific antigens may serve as targets against which tumor-destructive immune responses can be generated. MAGE-1 and %%%MAGE%%-%%%3%% are two clinically relevant antigens expressed in many human melanomas and other tumors, but not in normal tissues, except testis. Here, we have investigated whether DNA and cellular vaccines against MAGE-1 and %%%MAGE%%-%%%3%% can induce antigen-specific anti-tumor immunity and cause rejection of MAGE-expressing tumors. **MATERIALS AND METHODS:** Mice were immunized against MAGE-1 and %%%MAGE%%-%%%3%% by subcutaneous injection of genetically modified embryonic fibroblasts or intramuscular injection of purified DNA. Mice were injected with lethal doses of B16 melanoma cells expressing the corresponding MAGE antigens or the unrelated protein SIV tat, and tumor development and survival were monitored. **RESULTS:** Intramuscular expression of MAGE-1 and %%%MAGE%%-%%%3%% by plasmid DNA injection and subcutaneous immunization with syngeneic mouse embryonic fibroblasts transduced with recombinant retroviruses to express these antigens induced specific immunity against tumors expressing MAGE-1 and %%%MAGE%%-%%%3%%. Both CD4+ and CD8+ T cells were required for anti-tumor immunity. Coexpression of granulocyte-macrophage colony-stimulating factor (%%GM%%-%%%CSF%%) or B7-1 significantly increased anti-tumor immunity in an antigen-specific manner and resulted in a considerable proportion of mice surviving lethal tumor challenge. **CONCLUSIONS:** Our results suggest that genetic and cellular vaccines against MAGE and other tumor antigens may be useful for the therapy of tumors expressing specific markers, and that %%GM%%-%%%CSF%% and B7-1 are potent stimulators for the induction of antigen-specific tumor immunity.

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WELCOME TO THE U.S. PATENT TEXT
FILE *****

=> s 424/93.21/ccls

L1 120 424/93.21/CCLS

=> s l1 and (gmcsf or gm(w)csf)

105 GMCSF
42802 GM
4014 CSF
1142 GM(W)CSF

L2 23 L1 AND (GMCSF OR GM(W)CSF)

=> s l2 and mage

196 MAGE
L3 1 L2 AND MAGE

=> d

1. 5,759,535, Jun. 2, 1998, Immunotherapeutic strategies for the treatment of cancer; Edward P. Cohen, **424/93.21**;
435/69.1, 172.3, 320.1 [IMAGE AVAILABLE]

=> d kwic

US PAT NO: 5,759,535 [IMAGE AVAILABLE] L3: 1
of 1 US-CL-CURRENT: **424/93.21**; 435/69.1, 172.3, 320.1

SUMMARY:

BSUM(3)

Only . . . gene products (e.g., p53); reactivated embryonic gene products not expressed in adult tissues (e.g., P91A found in the P815 mastocytoma); **MAGE** 1 (found in melanomas and human breast tumors); tissue specific self-antigens expressed by tumors (e.g., tyrosinase); and a variety of. . .

SUMMARY:

BSUM(6)

Many . . . et al., Int. J. Cancer 53:471-477 [1993]; interferon-.alpha., (IFN-.alpha.)(Porgador, A., et al., Int. Immunol 150:1458-1570 [1993]); granulocyte-macrophage colony stimulating factor (**GM**.**CSF**) (Dranoff, G., et al., Proc. Nat. Acad. Sci. USA 90:3539-3543 [1993]) and several others.

SUMMARY:

BSUM(7)

Immunizations . . . Int. J. Cancer 53:471-477 (1993), Karp, et al., J. Immunol 150:896-908 (1993)), IFN-.alpha.(Porgador

et al., J. Immunol 150:1458-1470 (1993)), or **GM**.**CSF** (Dranoff, et al., Proc. Natl. Acad. Sci. USA 90:3539-3543 (1993)), among others (Pardoll, et al., Curr. Opin. Immunol 4:619-623 (1992),. . .

DETDESC:

DETD(80)

Exemplary . . . (Blankenstein, et al. J. Exp. Med. 173: 1047-1052 [1991]); and interleukin-4 (Golubbeck, P. T., et al. Science 254: 713-716 [1991]) **GM**.**CSF** (Dranoff, G., et al., Proc. Nat. Acad. Sci. USA 90:3539-3543 [1993]) or other cytokines capable of augmenting an anti-tumor response. . .

=> d date

L3: 1 of 1 TITLE:

Immunotherapeutic strategies for the treatment of cancer US
PAT NO: 5,759,535 DATE ISSUED: Jun. 2,
1998 [IMAGE AVAILABLE]
APPL-NO: 08/242,405 DATE FILED: May 13,
1994
=> d his

(FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)

L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE

=> s l2 and melanoma

3543 MELANOMA
L4 8 L2 AND MELANOMA

=> d his

(FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)

L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE
L4 8 S L2 AND MELANOMA

=> d 1-8

1. 5,788,963, Aug. 4, 1998, Isolation and/or preservation of dendritic cells for prostate cancer immunotherapy; Gerald P. Murphy, et al., **424/93.21**; 185.1, 277.1 [IMAGE AVAILABLE]

2. 5,759,535, Jun. 2, 1998, Immunotherapeutic strategies for the treatment of cancer; Edward P. Cohen, **424/93.21**;
435/69.1, 172.3, 320.1 [IMAGE AVAILABLE]

3. 5,705,151, Jan. 6, 1998, Gene therapy for T cell regulation; Steve W. Dow, et al., **424/93.21**; 450; 435/7.2, 69.1, 172.3, 320.1; 514/44; 935/54, 55, 62, 71 [IMAGE AVAILABLE]

4. 5,702,702, Dec. 30, 1997, Modified cytotoxic tall cell line

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and compositions and methods for manufacture and use thereof as therapeutic reagents for cancer; Daniela Santoli, et al., 424/93.71, 93.1, 93.2, **93.21**, 93.7, 534; 435/2, 366, 372, 372.3; 514/2, 9, 10, 885; 552/576, 577, 581 [IMAGE AVAILABLE]

5. 5,683,690, Nov. 4, 1997, Modified cytotoxic cell line and compositions and methods for manufacture and use thereof as therapeutic reagents for cancer; Daniela Santoli, et al., 424/93.71, 93.1, 93.2, **93.21**, 93.7, 534; 435/2, 372.3, 375 [IMAGE AVAILABLE]

6. 5,637,483, Jun. 10, 1997, Irradiated tumor cell vaccine engineered to express **GM**--**CSF**; Glenn Dranoff, et al., **424/93.21**; 435/320.1; 514/44; 935/57, 62, 71 [IMAGE AVAILABLE]

7. 5,571,797, Nov. 5, 1996, Method of inducing gene expression by ionizing radiation; Tsuneya Ohno, et al., 514/44; 424/1.11, 1.49, 1.61, 1.65, 1.69, 93.2, **93.21**, 450; 435/69.1, 69.5, 172.3, 320.1; 536/24.1; 935/6, 34, 59, 62 [IMAGE AVAILABLE]

8. 5,470,730, Nov. 28, 1995, Method for producing T.sub.H-independent cytotoxic T lymphocytes; Phillip D. Greenberg, et al., 435/172.3; **424/93.21**; 435/69.1, 69.52, 70.4, 252.3, 320.1 [IMAGE AVAILABLE]
=> d fro 6

US PAT NO: 5,637,483 [IMAGE AVAILABLE] L4: 6
of 8 DATE ISSUED: Jun. 10, 1997

TITLE: Irradiated tumor cell vaccine engineered to express **GM**--**CSF**

INVENTOR: Glenn Dranoff, Lexington, MA
Richard C. Mulligan, Lincoln, MA
Drew Pardoll, Baltimore, MD

ASSIGNEE: Whitehead Institute for Biomedical Research, Cambridge, MA (U.S. corp.)

Johns Hopkins University School of Medicine, Baltimore, MD (U.S. corp.)

APPL-NO: 08/265,554

DATE FILED: Jun. 23, 1994

REL-US-DATA: Continuation of Ser. No. 956,621, Oct. 5, 1992, abandoned, which is a continuation-in-part of Ser. No. 771,194, Oct. 4, 1991, abandoned.

INT-CL: [6] A61K 48/00; C12N 15/00

US-CL-ISSUED: 424/93.21; 435/320.1; 514/44; 935/57, 62, 71 US-CL-CURRENT: **424/93.21**; 435/320.1; 514/44; 935/57, 62, 71 SEARCH-FLD: 424/93.21, 93.1, 93.2; 514/44; 435/320.1, 240.1 REF-CITED:

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5,078,996 1/1992 Conlon, III et al. 424/85.1

5,098,702 3/1992 Zimmerman et al. 424/85.21

FOREIGN PATENT DOCUMENTS
3 922 444 1/1991 Federal Republic of Germany

WO92/05262 4/1992 World Intellectual Property Organization

WO92/07573 5/1992 World Intellectual Property Organization

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ART-UNIT: 184

PRIM-EXMR: Jacqueline M. Stone

ASST-EXMR: Dale Curtis Hogue, Jr.

LEGAL-REP: Albert P. Pennie & Edmonds Halluin

ABSTRACT:

A method of altering the specific, systemic immune response of an individual to a target antigen by the co-administration of a cytokine an adhesion or accessory molecule and the target antigen. The target antigen may be a tumor cell, a tumor cell antigen, an infectious agent or other foreign antigen, or other antigens to which an enhanced systemic immune response is desirable. Alternatively, the antigen may be a non-foreign antigen when a suppression of a systemic immune response is desired. The resulting systemic immune response is specific for the target antigen. 17 Claims, 23 Drawing Figures

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(FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)

L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE
L4 8 S L2 AND MELANOMA

=> s l2 not (l3 or l4)

L5 15 L2 NOT (L3 OR L4)

=> d 1-15

1. 5,766,585, Jun. 16, 1998, Systemic gene treatment of connective tissue diseases with IRAP-1; Christopher H. Evans, et al., **424/93.21**, 93.1, 93.2, 529, 534; 435/172.3, 320.1; 514/44; 935/23, 71 [IMAGE AVAILABLE]

2. 5,763,415, Jun. 9, 1998, Destruction of the epithelium of an exocrine gland in the prophylactic and therapeutic treatment of cancer; Saraswati Vaidyanathan Sukumar, 514/44; 424/93.1, **93.21**, 435/69.1, 172.3, 235.1, 325; 514/2 [IMAGE AVAILABLE]

3. 5,744,122, Apr. 28, 1998, Diagnosis and treatment of cancer having clonal macrophage involvement; Michael S. McGrath, et al., 424/9.2, **93.21**, 435/5, 6, 69.1, 91.2, 91.33, 325, 366, 372; 514/44 [IMAGE AVAILABLE]

4. 5,741,486, Apr. 21, 1998, Safe vectors for gene therapy; Vinay K. Pathak, et al., **424/93.21**, 93.2 [IMAGE AVAILABLE]

5. 5,736,387, Apr. 7, 1998, Envelope fusion vectors for use in gene delivery; Ralph W. Paul, et al., 435/320.1; **424/93.21**, 435/6, 69.5, 69.51, 69.52, 69.7, 91.2, 325; 514/44; 530/350, 387.1; 536/23.5, 24.31 [IMAGE AVAILABLE]

6. 5,710,037, Jan. 20, 1998, Retroviral vector particles; Elio F. Vanin, et al., 435/325; 424/93.2, **93.21**, 435/320.1, 363, 366, 372; 536/23.72, 24.1 [IMAGE AVAILABLE]

7. 5,707,865, Jan. 13, 1998, Retroviral vectors for expression in embryonic cells; Donald B. Kohn, et al., 435/325; 424/93.1, 93.2, **93.21**, 435/172.3, 235.1, 320.1, 352, 354; 514/44; 536/23.1, 24.1; 935/22, 32, 66, 70 [IMAGE AVAILABLE]

8. 5,698,443, Dec. 16, 1997, Tissue specific viral vectors; Daniel Robert Henderson, et al., 435/320.1; **424/93.21**, 435/172.3, 252.3; 514/2, 44 [IMAGE AVAILABLE]

9. 5,688,773, Nov. 18, 1997, Method of selectively destroying neoplastic cells; E. Antonio Chiocca, et al., 514/44; 424/93.1, **93.21**, 435/172.3, 320.1 [IMAGE AVAILABLE]

10. 5,679,342, Oct. 21, 1997, Hepatitis C virus infected cell systems; Michael Houghton, et al., **424/93.21**, 189.1, 228.1; 435/5, 69.3, 70.3, 235.1, 239, 372.2, 372.3 [IMAGE AVAILABLE]

11. 5,672,493, Sep. 30, 1997, De novo induction of cells exhibiting characteristics of macrophages utilizing feline sarcoma virus; Levy Kopelovich, 435/172.3; 424/93.2, **93.21**, 435/366 [IMAGE AVAILABLE]

12. 5,652,130, Jul. 29, 1997, Retroviral vectors expressing tumor necrosis factor (TNF); Michael Kriegler, et al., 435/172.3; 424/93.2, **93.21**, 435/320.1, 366, 372 [IMAGE AVAILABLE]

13. 5,635,399, Jun. 3, 1997, Retroviral vectors expressing cytokines; Michael Kriegler, et al., 435/320.1; 424/93.2, **93.21**, 435/172.3 [IMAGE AVAILABLE]

14. 5,591,625, Jan. 7, 1997, Transduced mesenchymal stem cells; Stanton L. Gerson, et al., 435/366; **424/93.21**, 93.7; 435/172.3, 320.1; 935/62, 70, 71 [IMAGE AVAILABLE]

15. 5,574,205, Nov. 12, 1996, Homologous recombination for universal donor cells and chimeric mammalian hosts; Raju Kucherlapati, et al., 800/2; 424/9.2, **93.21**, 435/172.3, 320.1; 800/DIG.1, DIG.2; 935/62, 111 [IMAGE AVAILABLE]

=> d ab 9

US PAT NO: 5,688,773 [IMAGE AVAILABLE]

L5: 9

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ABSTRACT:

A method for selectively killing nervous system and peripheral neoplastic cells is provided. Viral vectors are used to selectively express a cytochrome P450 gene in neoplastic cells, whose gene product targets the cells for selective killing, by rendering the cells sensitive to a chemotherapeutic agent.

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(FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)

L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE
L4 8 S L2 AND MELANOMA
L5 15 S L2 NOT (L3 OR L4)

=> s mage()3

196 MAGE
2304355 3
L6 21 MAGE(W)3

=> s l6(p)melanoma

3543 MELANOMA
L7 11 L6(P)MELANOMA

=> d kwic

US PAT NO: 5,783,567 [IMAGE AVAILABLE] L7: 1
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SUMMARY:

BSUM(22)

TABLE 3

Tumor Antigens	Associated Antigen
Cancer	
Melanoma	BAGE 2-10
Breast/Ovarian	c-ERB2 (Her2/neu)
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-1
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-2
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-3. . . lymphoma/Hodgkin's lymphoma
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-4
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-6
Burkitt's lymphoma/Hodgkin's lymphoma	EBV
Burkitt's lymphoma/Hodgkin's lymphoma	EBV LMP2A
Melanoma	GAGE-1
Melanoma	gp75
Cervical	HPV 16 E6
Cervical	HPV 16 E7
Cervical	HPV 18 E6
Cervical	HPV 18 E7

Melanoma MAG
Melanoma MAGE-1
Melanoma MAGE-2
Melanoma **MAGE**-*3**
Melanoma MAGE-4b
Melanoma MAGE-5
Melanoma MAGE-6
Melanoma MART-1/Melan-A
Pancreatic/Breast/Ovarian
MUC-1
Melanoma MUM-1-B
Breast/Colorectal/Burkitt's lymphoma
p53
Melanoma Pmel 17 (gp100)
Prostate PSA Prostate Specific Antigen
Melanoma Tyrosinase
CEA Carcinoembryonic
Antigen
LRP Lung Resistance Protein
Bc1-2
Ki-67

=> s l7 and (gmcsf of gm()csf)

105 GMCSF
42802 GM
0 GMCSF OF GM
(GMCSF(1W)GM)
4014 CSF
0 GMCSF OF GM(W)CSF
L8 0 L7 AND (GMCSF OF GM(W)CSF)

=> s l7 and (gmcsf or gm()csf)

105 GMCSF
42802 GM
4014 CSF
1142 GM(W)CSF
L9 1 L7 AND (GMCSF OR GM(W)CSF)

=> d

1. 5,744,353, Apr. 28, 1998, Cytolytic T cell lines which bind to complexes of tumor rejection antigens and HLA-B44 molecules; Jean Herman, et al., 435/325, 372.3 [IMAGE AVAILABLE]

=> d date

L9: 1 of 1 TITLE:

Cytolytic T cell lines which bind to complexes of tumor rejection antigens and HLA-B44 molecules
US PAT NO: 5,744,353 DATE ISSUED: Apr. 28, 1998 [IMAGE AVAILABLE]
APPL-NO: 08/796,883 DATE FILED: Feb. 6, 1997 REL-US-DATA: Division of Ser. No. 602,506, Feb. 20, 1996, which is a continuation-in-part of Ser. No. 531,864, Sep. 21, 1995, which is a continuation-in-part of Ser. No. 373,636, Jan. 17, 1995, which is a continuation-in-part of Ser. No.

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253,503, Jun. 3, 1994, Pat. No. 5,589,334.
=> d ab

US PAT NO: 5,744,353 [IMAGE AVAILABLE] L9: 1
of 1

ABSTRACT:

Tumor rejection antigens presented by HLA-B44 molecules are described. These peptides are useful in diagnostic and therapeutic methodologies. The tumor rejection antigens are derived from MAGE tumor rejection antigen precursors.

=> d his

(FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)

L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE
L4 8 S L2 AND MELANOMA
L5 15 S L2 NOT (L3 OR L4)
L6 21 S MAGE()3
L7 11 S L6(P)MELANOMA
L8 0 S L7 AND (GMCSF OF GM()CSF)
L9 1 S L7 AND (GMCSF OR GM()CSF)

=> s l7 not l9

L10 10 L7 NOT L9

=> d 1-10

1. 5,783,567, Jul. 21, 1998, Microparticles for delivery of nucleic acid; Mary Lynne Hedley, et al., 514/44; 435/320.1; 536/23.1 [IMAGE AVAILABLE]

2. 5,750,395, May 12, 1998, DNA encoding MAGE-1 C-terminal cytotoxic t lymphocyte immunogenic peptides; John D. Fikes, et al., 435/325, 69.3, 252.3, 254.2, 320.1; 536/23.5 [IMAGE AVAILABLE]

3. 5,695,994, Dec. 9, 1997, Isolated cytolytic T cells specific for complexes of MAGE related peptides and HLA molecules; Thierry Boon-Falleur, et al., 435/325, 355, 372.3; 530/328 [IMAGE AVAILABLE]

4. 5,662,907, Sep. 2, 1997, Induction of anti-tumor cytotoxic T lymphocytes in humans using synthetic peptide epitopes; Ralph T. Kubo, et al., 424/195.1, 193.1, 197.11, 277.1; 530/300, 328, 403 [IMAGE AVAILABLE]

5. 5,612,201, Mar. 18, 1997, Isolated nucleic acid molecules useful in determining expression of a tumor rejection antigen precursor; Etienne De Plaen, et al., 435/91.2, 6; 536/23.1, 24.33 [IMAGE AVAILABLE]

6. 5,591,430, Jan. 7, 1997, Isolated, MAGE-3 derived peptides which complex with HLA-A2 molecules and uses thereof; Alan Townsend, et al., 424/93.71, 185.1, 277.1; 435/7.24, 372.3; 530/328, 395, 828 [IMAGE AVAILABLE]

7. 5,541,104, Jul. 30, 1996, Monoclonal antibodies which bind to tumor rejection antigen precursor mage-1; Yao-Tseng Chen, et al., 435/344.1; 424/138.1, 155.1, 174.1; 435/69.6, 70.21, 172.2; 530/350, 387.7, 388.8; 935/15 [IMAGE AVAILABLE]

8. 5,512,444, Apr. 30, 1996, Method for determining bladder tumors by assaying for MAGE-1,2,3 or 4; Jean-Jacques Patard, et al., 435/6, 7.1, 7.9, 91.2; 536/23.1, 24.3 [IMAGE AVAILABLE]

9. 5,462,871, Oct. 31, 1995, Isolated nucleic acid molecules which encode MAGE derived nonapeptides; Thierry Boon-Falleur, et al., 435/354, 252.3, 365; 536/23.1, 23.5 [IMAGE AVAILABLE]

10. 5,342,774, Aug. 30, 1994, Nucleotide sequence encoding the tumor rejection antigen precursor, MAGE-1; Thierry Boon, et al., 435/371, 69.1, 69.3, 172.3, 235.1, 252.3, 320.1; 530/350; 536/23.5; 935/9, 32, 34, 57, 62, 70, 71 [IMAGE AVAILABLE]

=> d kwic

US PAT NO: 5,783,567 [IMAGE AVAILABLE] L10:
1 of 10
SUMMARY:

BSUM(22)

TABLE 3

Tumor Antigens	
Cancer	Associated Antigen
Melanoma	
Breast/Ovarian	BAGE 2-10
Burkitt's lymphoma/Hodgkin's lymphoma	c-ERB2 (Her2/neu)
	EBNA-1
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-2
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-3. . . lymphoma/Hodgkin's lymphoma
	EBNA-4
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-6
Burkitt's lymphoma/Hodgkin's lymphoma	EBV
Burkitt's lymphoma/Hodgkin's lymphoma	EBV LMP2A
Melanoma	GAGE-1
Melanoma	gp75
Cervical	HPV 16 E6
Cervical	HPV 16 E7
Cervical	HPV 18 E6
Cervical	HPV 18 E7
Melanoma	MAG
Melanoma	MAGE-1
Melanoma	MAGE-2
Melanoma	**MAGE**..**3**
Melanoma	MAGE-4b
Melanoma	MAGE-5
Melanoma	MAGE-6
Melanoma	MART-1/Melan-A
Pancreatic/Breast/Ovarian	MUC-1
Melanoma	MUM-1-B

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Breast/Colorectal/Burkitt's lymphoma
p53
Melanoma Pmel 17 (gp100)
Prostate PSA Prostate Specific Antigen
Melanoma Tyrosinase
CEA Carcinoembryonic
Antigen
LRP Lung Resistance Protein
Bc1-2
Ki-67

=> d kwic 2-10

US PAT NO: 5,750,395 [IMAGE AVAILABLE] L10:
2 of 10
SUMMARY:

BSUM(5)

More recently a new family of antigens has been described on
melanoma tumors. These antigens, now termed the
***melanoma** antigen," or MAGE family of antigens, were
identified in a **melanoma** cell line which was lysed by a
panel of autologous cytotoxic T lymphocytes ("CTLs"). Cells
which did not express a . . . any significant homology with any
sequence in data banks, including GenBank. Two additional
nonidentical cDNAs were also found (MAGE-2 and
MAGE-*3***) which were more closely related to each other
than to MAGE-1, but the three were approximately equally
expressed.

US PAT NO: 5,695,994 [IMAGE AVAILABLE] L10:
3 of 10
DETDDESC:

DETD(55)

As . . . gene and more than one MAGE antigen coding
sequence. Given the finding that both a MAGE-1 derived
nonapeptide and a **MAGE**-*3** derived nonapeptide are
presented by a common HLA molecule supports this
contention. Such cells may be regarded as universal effector. .
. combined with a suitable adjuvant, such as those well known
to the art. Treatment of various cancerous conditions, such as
melanoma and breast cancer, may be carried out using
these transfectant.

US PAT NO: 5,662,907 [IMAGE AVAILABLE] L10:
4 of 10

ABSTRACT:

The . . . treating cancer. The invention provides peptides
based on a 9 residue epitope derived from the product of the
tumor-associated gene **MAGE**-*3**. The peptide induces
CTL that kill **melanoma** and other tumor cells lines.

SUMMARY:

BSUM(6)

In contrast with the somewhat limited frequency of expression
of MAGE-1, the MAGE-2 and **MAGE**-*3** genes are
expressed in approximately 80-90% of the **melanoma** lines
examined, and also in the other tumor types such as breast,

colon, lung and thyroid cancers (Zakut et al. (1990) Cancer
Res. 53:5-8). Thus, it would be attractive to identify peptides
derived from the MAGE-2 or **MAGE**-*3** gene products
which could serve as CTL antigens.

SUMMARY:

BSUM(9)

The . . . a protein comprising an epitope having the
sequence EVDPIGHLY (SEQ ID NO.:2). The cells are usually
tumor cells, such as **melanoma** cells expressing a protein
product of the **MAGE**-*3** gene. The peptides of the
invention usually consist essentially of about 8 to about 10
residues and have the sequence. . .

DRAWING DESC:

DRWD(3)

FIGS. 2A and 2B show antigen-specificity and
MHC-restriction analysis of **MAGE**-*3**-reactive CTL. FIG.
2A shows cytotoxic responses using peptide-loaded target cells
and **melanoma** tumors: (.circle-solid.), Steinlin (HLA
homozygous, Epstein-Barr Virus-transformed lymphoblastoid
cell line, HLA-A1/1, -B8/8) pulsed with **MAGE**-*3** peptide
EVDPIGHLY (SEQ ID NO.:2); (.tangle-solidup.), Steinlin cells
pulsed with MAGE-1 peptide EADPTGHSY (SEQ ID NO.:1);
(.largecircle.), Steinlin cells with no peptide; (.tangle-soliddn.),
mel-397 (HLA-A1/25, **MAGE**-*3**+); (.DELTA.), mel-938
(HLA-A1/24, -B7/8, **MAGE**-*3**+); (.diamond.), mel-888
(HLA-A1/24, -B22/52, -Cw1/w7 **MAGE**-*3**+);
(.diamond-solid.), mel-888 pulsed with **MAGE**-*3** peptide
EVDPIGHLY (SEQ ID NO.:2); (.gradient.), mel-526
(HLA-A2/3, -B50/62, -Cw3, **MAGE**-*3**+). FIG. 2A
demonstrates that CTLs induced with peptide EVDPIGHLY
(SEQ ID NO.:2) can specifically kill
MAGE-*3**-expressing **melanoma** tumor cells.

DRAWING DESC:

DRWD(5)

FIG. 3 shows cytotoxic activity of **MAGE**-*3**-specific
CTL towards various tumors. The **MAGE**-*3** specific
CTL was tested for its ability to kill breast and prostate
HLA-A1+ tumor lines previously treated, or not, with
.gamma.-IFN. Cytotoxic responses were measured against:
(.circle-solid.), mel-397 **MAGE**-*3**+); (.largecircle.),
mel-397 plus .gamma.-IFN; (.box-solid.) HBL-100
(HLA-A1/10, -B7/8 **MAGE**-*3**+); (.quadrature.) HBL-100
plus .gamma.-IFN; (.tangle-solidup.), BT-20 (HLA-A1,
-B16, **MAGE**-*3**+); (.DELTA.), BT-20 plus .gamma.-IFN;
(.box-solid.), PC3 HLA-A1/9; (.diamond.), PC3 plus
.gamma.-IFN; (.tangle-soliddn.) mel-888 plus .gamma.-IFN
(**MAGE**-*3**+.sup.-). FIG. 3 demonstrates that
MAGE-*3**-specific CTL can kill tumors other than
melanoma which express the **MAGE**-*3** gene
product.

DETDDESC:

DETD(4)

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Synthetic peptides disclosed here can be used therapeutically to elicit CTL responses to **melanoma**, breast, colon, prostate, or other cells which express proteins (such as the **MAGE**¹-**3** or MAGE-2 gene products) having the EVDPIGHLY (SEQ ID NO.:2) epitope. This approach can be used therapeutically either in the . . .

DETDESC:

DETD(29)

The . . . to treat and/or prevent cancer. Examples of diseases which can be treated using the immunogenic peptides of the invention include **melanoma**, breast, colon, lung, and thyroid cancers. The expression of the **MAGE**¹-**3** gene can be determined using standard techniques such as measuring the presence of **MAGE**¹-**3** mRNA in the tumor cells, for example by PCR or Northern blot analysis.

DETDESC:

DETD(73)

Induction . . . the synthetic peptides. Out of the 6 peptides studied only one, the highest MHC binder (EVDPIGHLY (SEQ ID NO.:2)), from **MAGE**¹-**3** was able to elicit CTL in one of the blood donors. After 2 rounds of stimulation in culture with autologous. . . NO.:2), significant cytotoxic activity towards peptide-sensitized, HLA-A1-bearing target cells was observed (FIG. 2a). More significant was the observation that two **MAGE**¹-**3** -expressing HLA-A1 **melanoma** cell lines (397-mel and 938-mel, Zakut et al. (1990) Cancer Res. 53:5-8) were also killed by these CTL (FIG. 2a).. . .

DETDESC:

DETD(74)

Antigen Specificity and MHC Restriction Analysis. The CTL response appeared to be specific and HLA-A1-restricted, since HLA-A1 **melanoma** cells negative for **MAGE**¹-**3** (mel-888), and **melanoma** cells that expressed **MAGE**¹-**3**, but of a different HLA-A allelic type (mel-526, HLA-A2/A3 Zakut et al., supra) were not lysed by the CTL line. The exogenous addition of the peptide EVDPIGHLY to the **MAGE**¹-**3**⁻ negative, HLA-A1-positive mel-888 cell line rendered the cells susceptible to lysis by the CTL (FIG. 2a, insert), indicating that this tumor. . .

DETDESC:

DETD(76)

Cytolytic Activity to Non-**Melanoma** Tumors. As mentioned above, other tumors besides melanomas can also express MAGE genes, in particular MAGE-2 and -3. The ability of the **MAGE**¹-**3**⁻ specific CTL line to kill HLA-A1-expressing breast and prostate carcinoma cell lines was also tested. The results in FIG. 3 show that one of the two breast cancer cell lines (HBL-100), reported to express **MAGE**¹-**3** (Zakut et al., supra), was highly susceptible to lysis by the CTL. The level of lysis improved significantly if these. . . of MHC class I

molecules on the cell surface. The other breast cancer cell line (BT-20), also reported to express **MAGE**¹-**3** (Zakut et al., supra), and the prostate cancer line (PC3) were also killed, but to a lesser extent, and only. . .

US PAT NO: 5,612,201 [IMAGE AVAILABLE] L10: 5 of 10

DETDESC:

DETD(133)

In . . . lymphocytes of the same patient. Also negative were several normal tissues of other individuals (FIG. 10 and FIG. 11). Fourteen **melanoma** cell lines of other patients were tested. Eleven were positive with bands of varying intensities. In addition to these culture cell lines, four samples of **melanoma** tumor tissue were analyzed. Two samples, including a metastasis of patient MZ2 proved positive, excluding the possibility that expression of. . . that showed complete specificity for one of the three genes (FIG. 9). Control experiments carried out by diluting RNA of **melanoma** MZ2-MEL 3.0 in RNA from negative cells indicated that under the conditions used herein the intensity of the signal decreased. . . expression of the three MAGE genes, suggesting therefore a level of expression of less than 1/300.sup.th that of the MZ2 **melanoma** cell line (FIG. 11). For the panel of **melanoma** cell lines, the results clearly showed that some melanomas expressed MAGE genes mage 1, 2 and 3 whereas other expressed. . . 10). Some of the other tumors also expressed all three genes whereas others expressed only mage-2 and 3 or only **mage**¹-**3**. It is impossible to exclude formally that some positive PCR results do not reflect the expression of one of the. . .

DETDESC:

DETD(179)

TABLE 3

		TNF pg/ml			
		Exp 1	Exp 2		
		Number	+CTL	+CTL Expression	
				Expression	
				of **Mage** ¹ -**3**	
				of HLA-A-1	
MZ2-MEL.61.2					
	50000	1	4	+++	+
MZ2-MEL-ET1					
	50000	>120	>120	+++	+
	1666	66.			

DETDESC:

DETD(233)

The identification of **MAGE**¹-**3** derived TRAs as being presented by HLA-A1 molecules suggests various therapeutic and diagnostic approaches. In a therapeutic context, e.g., the treatment of a disorder characterized by **MAGE**¹-**3**

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expression may be treated in a number of ways, "disorder" being used to refer to any pathological condition where **MAGE**-*3** TRAP is expressed, such as cancer (e.g., **melanoma**).

DEDESC:
DETD(237)

Adoptive . . . elaborated upon supra. The cells used in this approach may be those that normally express the complex, such as irradiated **melanoma** cells or cells transfected with one or both of the genes necessary for presentation of the complex. Chen et al., . . . HLA molecule while the TRA is presented without the need for further processing. Thus, one may treat disorders where a **MAGE**-*3** derived TRA is presented by HLA-A1 molecules, or by any HLA molecule.
US PAT NO: 5,591,430 [IMAGE AVAILABLE] L10:
6 of 10
DEDESC:

DETD(50)

In addition, **melanoma** cell lines which were known to express **MAGE**-*3** and which were HLA-A2.sup.+ were used. These cell lines are identified in the figures as LB 373, LB43, LB24 clone. . .
US PAT NO: 5,541,104 [IMAGE AVAILABLE] L10:
7 of 10
DEDESC:

DETD(26)

Monoclonal . . . present in MZ2-MEL 3.1 lysate, but not in lysates of either of the other two cell lines. When three additional **melanoma** lines were tested, only those which were typed as being MAGE-1 positive reacted with the mAb. Expression of MAGE-2 or **MAGE**-*3** was irrelevant.

US PAT NO: 5,512,444 [IMAGE AVAILABLE] L10:
8 of 10
DEDESC:

DETD(16)

Table . . . (nomenclature is explained below). Of 57 samples of primary transitional cell carcinoma, 21% expressed MAGE-1, 30% expressed MAGE-2, 35% expressed **MAGE**-*3**, and 33% expressed MAGE-4. Ta tumors and low grade T1 tumors expressed none of these, or expressed only a single. . . invasive tumors studied. Among the 29 superficial tumors, the proportion was only 28%. Results paralleled other results reported previously for **melanoma**, in that all but one of the tumors expressing MAGE-1 also expressed **MAGE**-*3**.

US PAT NO: 5,462,871 [IMAGE AVAILABLE] L10:
9 of 10
DEDESC:

DETD(38)

TABLE 1

TNF pg/ml	
Exp 1	Exp 2
Number of	
+CTL	+CTL
Expression	
Expression	
Melanoma cells - 20/38	
- 20/38	
of **MAGE**-*3**	
of HLA-A1	

MZ2-MEL-61.2				
50000	1	4	+++	+
MZ2-MEL-ET1				
50000	>120	>120		
			+++	+
1666.				

DEDESC:

DETD(56)

As . . . gene and more than one MAGE antigen coding sequence. Given the finding that both a MAGE-1 derived nonapeptide and a **MAGE**-*3** derived nonapeptide are presented by a common HLA molecule supports this contention. Such cells may be regarded as universal effector. . . combined with a suitable adjuvant, such as those well known to the art. Treatment of various cancerous conditions, such as **melanoma** and breast cancer, may be carried out using these transfectants.
US PAT NO: 5,342,774 [IMAGE AVAILABLE] L10:
10 of 10
DEDESC:

DETD(103)

In . . . lymphocytes of the same patient. Also negative were several normal tissues of other individuals (FIG. 13 and FIG. 14). Fourteen **melanoma** cell lines of other patients were tested. Eleven were positive with bands of varying intensities. In addition to these culture cell lines, four samples of **melanoma** tumor tissue were analyzed. Two samples, including a metastasis of patient MZ2 proved positive, excluding the possibility that expression of. . . that showed complete specificity for one of the three genes (FIG. 12). Control experiments carried out by diluting RNA of **melanoma** MZ2-MEL 3.0 in RNA from negative cells indicated that under the conditions used herein the intensity of the signal decreased. . . expression of the three MAGE genes, suggesting therefore a level of expression of less than 1/300.sup.th that of the MZ2 **melanoma** cell line (FIG. 14). For the panel of **melanoma** cell lines, the results clearly showed that some melanomas expressed MAGE genes mage 1, 2 and 3 whereas other expressed. . . 1). Some of the other tumors also expressed all three genes whereas others expressed only mage-2 and 3 or only **mage**-*3**. It is impossible to exclude formally that some positive PCR results do not reflect the expression of one of the. . .

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L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE
L4 8 S L2 AND MELANOMA
L5 15 S L2 NOT (L3 OR L4)
L6 21 S MAGE()3
L7 11 S L6(P)MELANOMA
L8 0 S L7 AND (GMCSF OF GM()CSF)
L9 1 S L7 AND (GMCSF OR GM()CSF)
L10 10 S L7 NOT L9

=> s (gmcsf or gm()csf)(p)(treatment)(p)(cancer or melanoma
or malignancy or tumor or tumour)

105 GMCSF
42802 GM
4014 CSF
379440 TREATMENT
22994 CANCER
3543 MELANOMA
1994 MALIGNANCY
18528 TUMOR
1654 TUMOUR

L11 105 (GMCSF OR
GM(W)CSF)(P)(TREATMENT)(P)(CANCER OR
MELANOMA OR MAL
IGNANCY OR TUMOR OR TUMOUR)

=> d kwic

US PAT NO: 5,789,441 [IMAGE AVAILABLE] L11:
1 of 105
SUMMARY:

BSUM(39)

In . . . present invention, there is also provided the use of a
LTB.sub.4 agent as an antiviral agent for the prophylaxis and
treatment of viral infections in humans and animals in
association with other agents including but not limited to
granulocyte-macrophage colony-stimulating factor
(**GM**--**CSF**), granulocyte colony stimulating factor
(G-CSF), macrophage colony stimulating factor (M-CSF),
interferons, **tumor** necrosis factor .alpha., interleukin-3 and
interleukin-5, which have been shown to prime leukocytes for
the synthesis of LTB.sub.4 or other. . .

=> d kwic 2

US PAT NO: 5,783,569 [IMAGE AVAILABLE] L11:
2 of 105
DETDESC:

DETD(26)

In . . . This property can be exploited in a therapeutic
regimen for use as an adjuvant in parallel with radiation or
chemotherapy **treatment**. Radiation and chemotherapy are
known to result in neutropenia (reduced polymorphonuclear
(PMN) leukocyte cell count) and thrombocytopenia (reduced

platelet count). At present, these conditions are treated by the
administration of colony-stimulating factors such as
GM--**CSF** and granulocyte colony-stimulating factor
(G-CSF). Such factors are effective in overcoming neutropenia,
but fail to impact upon thrombocytopenia. Thus, the. . .
minimize the development of thrombocytopenia which limits the
dose of the radiation or chemotherapeutic agent which is used
to treat **cancer**.

=> d kwic 3-105

US PAT NO: 5,776,095 [IMAGE AVAILABLE] L11:
3 of 105
DETDESC:

DETD(5)

A middle-age woman with advanced breast **cancer**,
including bone and bone marrow invasion, has an aliquot of her
bone marrow removed and harvested for regrafting after
clearing the marrow of the **cancer** cells in vitro. The bone
marrow in the patient is then destroyed by i.v. infusion of 20 mg
NP-2 monoclonal antibody F(ab').sub.2 labeled with 200 mCi
Rhenium-188 according to the method of Griffiths et al.
(**Cancer** Res. 51:4594, 1991). Approximately 3 weeks later,
there is evidence of severe bone marrow toxicity which requires
the infusion of the autologous bone marrow which was
previously cleared of **cancer** cells, in combination with
hematopoietic growth factor administration, in this case with
GM--**CSF** given repeatedly before and after marrow
grafting. Six weeks later, the patient has renewed bone marrow
function and an MN3-Fab'. . . m) bone marrow scan shows
good bone marrow imaging without evidence of metastatic
defects. She is now a candidate for **treatment** of other sites
of her metastatic breast **cancer**.

US PAT NO: 5,776,094 [IMAGE AVAILABLE] L11:
4 of 105
DETDESC:

DETD(5)

A middle-age woman with advanced breast **cancer**,
including bone and bone marrow invasion, has an aliquot of her
bone marrow removed and harvested for regrafting after
clearing the marrow of the **cancer** cells in vitro. The bone
marrow in the patient is then destroyed by i.v. infusion of 20 mg
NP-2 monoclonal antibody F(ab').sub.2 labeled with 200 mCi
Rhenium-188 according to the method of Griffiths et al.
(**Cancer** Res. 51:4594, 1991). Approximately 3 weeks later,
there is evidence of severe bone marrow toxicity which requires
the infusion of the autologous bone marrow which was
previously cleared of **cancer** cells, in combination with
hematopoietic growth factor administration, in this case with
GM--**CSF** given repeatedly before and after marrow
grafting. Six weeks later, the patient has renewed bone marrow
function and an MN3-Fab'. . . (Tc-99m) bone marrow scan
shows good bone marrow imaging without evidence of
metastatic defects. She is now a candidate for **treatment** of
other sites of her metastatic breast **cancer**.

US PAT NO: 5,776,093 [IMAGE AVAILABLE] L11:
5 of 105
DETDESC:

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DETD(5)

A middle-age woman with advanced breast **cancer**, including bone and bone marrow invasion, has an aliquot of her bone marrow removed and harvested for regrafting after clearing the marrow of the **cancer** cells in vitro. The bone marrow in the patient is then destroyed by i.v. infusion of 20 mg NP-2 monoclonal antibody F(ab').sub.2 labeled with 200 mCi Rhenium-188 according to the method of Griffiths et al. (**Cancer** Res. 51:4594, 1991). Approximately 3 weeks later, there is evidence of severe bone marrow toxicity which requires the infusion of the autologous bone marrow which was previously cleared of **cancer** cells, in combination with hematopoietic growth factor administration, in this case with **GM**--**CSF** given repeatedly before and after marrow grafting. Six weeks later, the patient has renewed bone marrow function and an MN3-Fab'. . . (Tc-99m) bone marrow scan shows good bone marrow imaging without evidence of metastatic defects. She is now a candidate for **treatment** of other sites of her metastatic breast **cancer**.

US PAT NO: 5,766,897 [IMAGE AVAILABLE] L11:
6 of 105
DETDESC:

DETD(151)

Where . . . may be found in U.S. Pat. Nos. 5,292,724 and 5,182,259; guidance for administration of human growth hormone (hGH) in the **treatment** of individuals intoxicated with poisonous substances may be found in U.S. Pat. Nos. 5,140,008 and 4,816,439; guidance for administration of hGH in the **treatment** of topical ulcers may be found in U.S. Pat. No. 5,006,509; guidance for administration of (EPO) for **treatment** of anemia and pulmonary administration of EPO may be found in U.S. Pat. No. 5,354,934; guidance for administration of EPO, **GM**--**CSF**, G-CSF, and multi-CSF for **treatment** of pancytopenia may be found in U.S. Pat. No. 5,198,417; guidance for administration of EPO for treating iron overload may be found in U.S. Pat. No. 5,013,718; guidance for administration of EPO in the **treatment** of hemoglobinopathies may be found in U.S. Pat. No. 4,965,251; guidance for administration of insulin the **treatment** of diabetes may be found in U.S. Pat. No. 4,478,822; guidance for delivery of asparaginase for **treatment** of neoplasms may be found in U.S. Pat. Nos. 4,478,822 and 4,474,752; guidance for administration of L-asparaginase in the **treatment** of tumors is found in U.S. Pat. No. 5,290,773; guidance for administration of prostaglandin E1, prostaglandin E2, prostaglandin F2 alpha, . . . chymopapain, bromelain, chymotrypsin, streptokinase, urokinase, tissue plasminogen activator, fibrinolysin, deoxyribonuclease, siltalains, collagenase, asparaginase, or heparin in a cryogel bandage for **treatment** of sites of trauma may be found in U.S. Pat. No. 5,260,066; guidance for the administration of superoxide dismutase, glucocerebrosides, . . . deaminase, interferons (alpha, beta, and gamma), interleukin (1,2,3,4,5,6,7), tissue necrosis factor (TNF-alpha or TNF-beta), and colony stimulating factors (CSF, G-CSF, **GM**--**CSF**) in liposomes may be found in U.S. Pat. No. 5,225,212; guidance for administration of asparaginase or insulin in the **treatment** of neoplastic lesions may be found in U.S. Pat. No. 4,978,332; guidance for

administration of asparaginase in the reduction of **tumor** growth may be found in U.S. Pat. No. 4,863,910; guidance for the administration of antibodies in the prevention of transplant. . . cells, augmentation of natural killer cell activity, induction of interferon-gamma, restoration or enhancement of cellular immunity, and augmentation of cell-mediated anti-**tumor** activity may be found in U.S. Pat. No. 5,206,344; guidance for the administration of interleukin-2 in the **treatment** of tumors may be found in U.S. Pat. No. 4,690,915; and guidance for administration of interleukin-3 in the stimulation of hematopoiesis, as a **cancer** chemotherapy, and in the **treatment** of immune disorders may be found in U.S. Pat. No. 5,166,322.

US PAT NO: 5,763,415 [IMAGE AVAILABLE] L11:
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DETDESC:

DETD(16)

The present invention also provides a method of treating the ductal epithelium of a mammary gland both therapeutically and prophylactically for **cancer**. The method comprises treating the mammary gland therapeutically with any given therapeutic method, such as those currently known and used. . . the cancerous tissue, radiation therapy and chemotherapy. The method further comprises contacting, either concomitantly with or subsequently to the therapeutic **treatment**, the ductal epithelium of the mammary gland, e.g., by ductal cannulation, with an epithelium-destroying agent, which preferably does not specifically target cancerous cells, so as to destroy any remaining cancerous cells and noncancerous cells and inhibit the spread of **cancer**. The epithelium-destroying agent is preferably a vector comprising a thymidine kinase gene, such as a Herpes simplex thymidine kinase gene, . . . or ethanol. The method can additionally comprise contacting the ductal epithelium with a cytokine or hematopoietic growth factor, such as **GM**--**CSF**.

US PAT NO: 5,750,529 [IMAGE AVAILABLE] L11:
8 of 105
SUMMARY:

BSUM(11)

Recently, **cancer** **treatment** with anti-Apo-I antibody has been attempted as an apoptosis-related therapy. Among the myelodysplastic syndrome (MDS), refractory anemia (RA) and refractory. . . be treated with a combination of retinoic acid or vitamin D.sub.3, which is a differentiation inducer for hemopoietic cells, and **GM**--**CSF** or IL-3 as an apoptosis regulating agent which suppresses excessive apoptosis of platelet producing cells whereas, in RAEB (refractory anemia. . .

US PAT NO: 5,739,110 [IMAGE AVAILABLE] L11:
9 of 105
DETDESC:

DETD(6)

Interleukin-1 . . . Immunol. 140:3830, 1988; Futami, H., et al., J. Immunol. 145:4121, 1990; Fibbe, W. E., et al., Exp. Hematol. 17:805, 1989). **GM**--**CSF** and G-CSF have

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also been found to have marked restorative effects after irradiation (Tanikawa, S., et al., Exp. Hematol. 17:883, 1989; Schuening, F. G., et al., Blood 74:1308, 1989) or ****treatment**** with chemotherapeutic drugs both in preclinical models (Moore, M. A. S., et al., Proc. Natl. Acad. Sci. USA 84:7134, 1987; . . . Welte, K., et al., J. Exp. Med. 165:941, 1987), as well as in human trials (Steward, W. P., et al., ****Cancer**** Treat. Rev. 17:77, 1990; Gianni, A. M., et al., J. Clin. Oncol. 8:768, 1990).

US PAT NO: 5,726,181 [IMAGE AVAILABLE] L11:
10 of 105
SUMMARY:

BSUM(117)

A further embodiment of claimed HLCD is a method of ****treatment**** of ****cancer**** in humans with convergent therapy or combination therapy. This method uses HLCD dissolved in NMP, in the presence of pharmaceutically. . . bleomycin, mitomycin-C, fluoxymesterone, mechlorethamine, teniposide, hexamethylmelamine, leucovorin, melphelan, methotrexate, mercaptopurine, mitoxantrone, BCNU, CCNU, procarbazine, vincristine, vinblastine, vindesine, thioTEPA, amsacrine, G-CSF, ****GM**--**CSF****, erythropoietin, .gamma.-methylene-10-deazaaminopterin or .gamma.-methylene-10-ethyl-10-deazaaminopterin, taxol, and 5-azacytidine. For the purpose of this invention, the terms convergent, co-administered, and combination are. . .

US PAT NO: 5,725,850 [IMAGE AVAILABLE] L11:
11 of 105
SUMMARY:

BSUM(6)

****GM**--**CSF**** is described by Gough, et al, Nature (1984) 309:763-767. This protein is further described in W087/02060, published 9 Apr. 1987 as being useful to treat ****cancer**** patients to regenerate leukocytes after traditional ****cancer**** ****treatment****, and to reduce the likelihood of viral, bacterial, fungal and parasitic infection, such as acquired immune deficiency syndrome (AIDS). Human. . .

US PAT NO: 5,720,952 [IMAGE AVAILABLE] L11:
12 of 105
CLAIMS:

CLMS(4)

4. The method of claim 3, wherein said ****GM**--**CSF**** protein is administered to a mammal with ****cancer**** following chemotherapeutic or irradiation ****treatment**** of said ****cancer****.

US PAT NO: 5,716,981 [IMAGE AVAILABLE] L11:
13 of 105
SUMMARY:

BSUM(7)

Lymphokines have also been utilized in the ****treatment**** of ****cancer****. Briefly, lymphokines are secreted by a variety of cells, and generally have an effect on specific cells in the

generation. . . response. Examples of lymphokines include Interleukins (IL)-1, -2, -3, and -4, as well as colony stimulating factors such as G-CSF, ****GM**--**CSF****, and M-CSF. Recently, one group has utilized IL-2 to stimulate peripheral blood cells in order to expand and produce large quantities of cells which are cytotoxic to ****tumor**** cells (Rosenberg et al., N. Engl. J. Med. 313:1485-1492, 1985).

US PAT NO: 5,705,151 [IMAGE AVAILABLE] L11:
14 of 105
DETDDESC:

DETD(110)

This example describes the ****treatment**** of canine ****melanoma**** with DNA encoding superantigen or ****GM**--**CSF****.

DETDDESC:

DETD(116)

TABLE 1

Patient Log for SEB.S and PCR.sub.3 -GM DNA
****Treatment**** of Canine ****Melanoma****

Patient	Stage	TN	**Tumor**	Size	Start Date	Response	Comments
Zomax	I	T1b	NOMO	1.5 cm diam	5/16/94	CR 51 wks	SEB.S + **GM**--**CSF**
Shadow	III	T2b	N1bMO	3 cm diam	5/23/94	CR 50 wks	SEB.S + **GM**--**CSF**
NG	I	T1	NOMO	1.2 cm diam	9/12/94	CR 34 wks	SEB.S + **GM**--**CSF**
Maggie	II	T2a	NOMO	2 cm diam	8/24/94	PR 33 wks	SEB.S + **GM**--**CSF**
K. C.	III	T3a	NOMO	>4 cm diam			

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10/13/94
SD 12 wk
SEB.S + **GM**--**CSF**

Belvedere
III
T2N1bMO
4 cm diam
10/13/94
CR 30 wks
SEB.S + **GM**--**CSF**

Nicholas
III
T3bNOMO
>4 cm diam
2/15/95
SD 12 wks
SEB.S + **GM**--**CSF**

Heidi
III
TON1bMO
LN: 2 cm diam
2/27/95
PR 10 wks
SEB.S + **GM**--**CSF**

Bear III
TON1bMO
LN: 2.5 cm
4/11/95
SD 4 wks
SEB.S + **GM**--**CSF**

Key to terminology in patient data sheets:

Stage: I represents the smallest and III the largest size, with metastase

TNM: World Health Organization staging system

SD = stable disease (no **tumor** growth)

PR = partial remission (>50% decrease in **tumor** size)

CR = **tumor** completely regressed

PD = progressive disease, no response to **treatment**

MCT = mast cell **tumor**

Mammary CA = mammary gland adenocarcinoma (malignant breast **cancer**)

Thyroid CA = thyroid adenocarcinoma

SCC = squamous cell carcinoma

DETDESC:

DETD(117)

The results shown in Table 1 indicate that a **treatment** response was observed in 6 of 9 dogs treated for the 12 week trial period. This included 4 complete remissions (no residual **tumor**) and 2 partial remissions (greater than 50% reduction in **tumor** size). Tumors in the remaining two dogs did not regress, but also did not progress in size during the 12 week trial. On average, a **tumor** response required 6 to 10 weeks to become apparent. The injections did not cause any inflammation or necrosis at injections. . . this study. These results provide evidence of the efficacy of direct DNA injection using DNA encoding superantigen (SEB) and cytokine (**GM**--**CSF**) for **treatment** of spontaneous malignant **melanoma** in an outbred species.

DETDESC:

DETD(122)

TABLE 2

Patient Log for SEB.S or PCR.sub.3 -GM DNA alone

Treatment of Canine **Melanoma**

Patient	Stage	TN	**Tumor** Size	Start Date	Response	Comments
---------	-------	----	----------------	------------	----------	----------

Jessie	II	T2bNOMO	2 cm diam	1/11/95	PD. . . 12 wks	SEB.S alone
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Scooter	I	T2aNOMO	2 cm diam	3/24/95	PD 7 wks	**GM**--**CSF** alone
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DETDESC:

DETD(125)

This example describes the **treatment** of various **tumor** types with superantigen or **GM**--**CSF** encoding DNA.

DETDESC:

DETD(128)

TABLE 3

Patient Log for SEB.S and PCR.sub.3 -GM DNA

Treatment of Various Carcinomas

Patient	**Tumor** Type	Stage	TN	**Tumor** Size	Start Date	Response	Comments
---------	----------------	-------	----	----------------	------------	----------	----------

Emma	Mammary CA	III	T4N1bNMO	1.8 cm diam	8/11/94		
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PR 22 wks
SEB.S + **GM**-*CSF** Baby

Mammary CA
II T1aN1bMO
2.6 cm diam
9/12/94
PR 8 wks
SEB.S + **GM**-*CSF** Christa

MCT IIIa
NA >2 cm diam
7/27/94
SD 39 wks
SEB.S + **GM**-*CSF** Jack

MCT IIIa
NA >3 cm diam
3/28/95
PD 4 wks
SEB.S + **GM**-*CSF** Britt

Thyroid CA
III
T3bNOMO
>7 cm diam
10/14/94
SD 16 wk
SEB.S + **GM**-*CSF** Duncan

Melanoma Toe
NA*
T2N1MO
>4 cm diam
8/11/94
SD 20 wks
SEB.S + **GM**-*CSF** Billy

Melanoma Toe
NA*
TON1bMO
LN 3.5 cm
1/10/95
CR 17 wks
SEB.S + **GM**-*CSF** Scotche

SCC Tonsil
NA T3NOMO
4 cm diam
3/27/95
SD SEB.S + **GM**-*CSF**

*Metastases
NA Not Applicable
CA Carcinoma
MCT Mast Cell **Tumor**
SCC Squamous Cell Carcinoma

US PAT NO: 5,702,919 [IMAGE AVAILABLE] L11:
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DETDESC:
DETD(34)

The in vivo effect of **GM**-*CSF** on megakaryocytes and platelets is not well delineated. Platelet counts varied in different animal studies with no changes observed in. . . treated with hGM-CSF [25,51,53] (Farese, A.). Thrombocytopenia has been reported as a complication in

several clinical studies of patients with **cancer** or acquired immunodeficiency syndrome receiving hGM-CSF [52-54]. The possibility of exacerbation of an otherwise stable or subclinical autoimmune thrombocytopenia was. . . also been reported in patients with aplastic anemia that platelet counts 1 hour after platelet transfusion were lower, while on **treatment** with hGM-CSF, were comparable to pre-**treatment** increments [55]. Other studies have shown no significant change, or, in some patients with myelodysplasia, an increase in platelet counts. . .

US PAT NO: 5,697,902 [IMAGE AVAILABLE] L11:
16 of 105
DETDESC:

DETD(5)

A middle-age woman with advanced breast **cancer**, including bone and bone marrow invasion, has an aliquot of her bone marrow removed and harvested for regrafting after clearing the marrow of the **cancer** cells in vitro. The bone marrow in the patient is then destroyed by i.v. infusion of 20 mg NP-2 monoclonal antibody F(ab').sub.2 labeled with 200 mCi Rhenium-188 according to the method of Griffiths et al. (**Cancer** Res. 51:4594, 1991). Approximately 3 weeks later, there is evidence of severe bone marrow toxicity which requires the infusion of the autologous bone marrow which was previously cleared of **cancer** cells, in combination with hematopoietic growth factor administration, in this case with **GM**-*CSF** given repeatedly before and after marrow grafting. Six weeks later, the patient has renewed bone marrow function and an MN3-Fab'. . . (Tc-99m) bone marrow scan shows good bone marrow imaging without evidence of metastatic defects. She is now a candidate for **treatment** of other sites of her metastatic breast **cancer**.

US PAT NO: 5,693,522 [IMAGE AVAILABLE] L11:
17 of 105
SUMMARY:

BSUM(7)

Lymphokines have also been utilized in the **treatment** of **cancer**. Briefly, lymphokines are secreted by a variety of cells, and generally have an effect on specific cells in the generation. . . response. Examples of lymphokines include Interleukins (IL)-1, -2, -3, and -4, as well as colony stimulating factors such as G-CSF, **GM**-*CSF**, and M-CSF. Recently, one group has utilized IL-2 to stimulate peripheral blood cells in order to expand and produce large quantities of cells which are cytotoxic to **tumor** cells (Rosenberg et al., N. Engl. J. Med. 323:1485-1492, 1985).

US PAT NO: 5,691,341 [IMAGE AVAILABLE] L11:
18 of 105
SUMMARY:

BSUM(18)

Recently, **cancer** **treatment** with anti-Apo-I anti-body has been attempted as an apoptosis-related therapy. Among the myelodysplastic syndrome (MDS), refractory anemia (RA) and refractory. . . treated with a combination of retinoic acid or active-type vitamin D.sub.3, which is a differentiation inducer for hemopoietic cells, and **GM**-*CSF** or IL-3 as an

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apoptosis regulating agent which suppresses excessive apoptosis of platelet producing cells whereas, in RAEB (refractory anemia. . .

US PAT NO: 5,681,719 [IMAGE AVAILABLE] L11:
19 of 105
SUMMARY:

BSUM(13)

Human and murine **GM**-*CSF**, which is a CSF protein of a different subclass, has been purified and the cDNAs cloned. This protein was shown to be distinct from other CSFs, e.g., CSF-1 (18). This **GM**-*CSF** protein is further described in PCT No. WO87/02060, published Apr. 9, 1987, as being useful to treat **cancer** patients to regenerate leukocytes after traditional **cancer** **treatment**, and to reduce the likelihood of viral, bacterial, fungal, and parasitic infection, such as in acquired immune deficiency syndrome (AIDS).

US PAT NO: 5,674,874 [IMAGE AVAILABLE] L11:
20 of 105
SUMMARY:

BSUM(147)

A further aspect of this invention is that HECPT is a method of **treatment** of **cancer** in humans with convergent therapy or combination drug therapy. This method uses 7-ethyl-10-hydroxy camptothecin dissolved in dimethylisobutyl alcohol (DMI) or dimethylacetamide. . . bleomycin, mitomycin-C, flouxymesterone, mechlorethamine, teniposide, hexamethylmelamine, leucovorin, melphalan, methotrexate, mercaptopurine, mitoxantrone, BCNU, CCNU, procarbazine, vincristine, vinblastine, vindesine, thioTEPA, amsacrine, G-CSF, **GM**-*CSF**, erythropoietin, sub-.gamma.-methylene-10-deazaaminopterin or sub-.gamma.-methylene-10-ethyl-10-deazaaminopterin, taxol, and 5-azacytidine. For the purpose of this invention, the terms convergent, co-administered, and combination are. . .

US PAT NO: 5,674,873 [IMAGE AVAILABLE] L11:
21 of 105
SUMMARY:

BSUM(108)

A further embodiment of claimed HECPT is a method of **treatment** of **cancer** in humans with convergent therapy or combination therapy. This method uses 10-hydroxy 7-ethyl camptothecin dissolved in dimethylisobutyl alcohol (DMI) or dimethylacetamide. . . bleomycin, mitomycin-C, flouxymesterone, mechlorethamine, teniposide, hexamethylmelamine, leucovorin, melphalan, methotrexate, mercaptopurine, mitoxantrone, BCNU, CCNU, procarbazine, vincristine, vinblastine, vindesine, thioTEPA, amsacrine, G-CSF, **GM**-*CSF**, erythropoietin, .gamma.-methylene-10-deazaaminopterin or .gamma.-methylene-10-ethyl-10-deazaaminopterin, taxol, and 5-azacytidine. For the purpose of this invention, the terms convergent, co-administered, and combination are. . .

US PAT NO: 5,674,694 [IMAGE AVAILABLE] L11:
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CLAIMS:

CLMS(16)

16. A method for determining the effectiveness of a bone marrow **treatment** technique comprising, testing a specimen of bone marrow cells prior to a **treatment** (pre-**treatment** cells) and a specimen of bone marrow cells after a **treatment** (post-**treatment** cells) for **tumor** cells of interest by:

(a) plating each specimen on homogeneous culture media which supports growth of bone marrow cells comprising. . . factor which stimulates the growth of cells of interest wherein the growth factor is selected from the group consisting of **GM**-*CSF** at a concentration of about 20 to about 150 U/ml of media, EGF at a concentration of about 1 to. . . number of individual clones of cells of interest, resulting from the culturing of each specimen; wherein,
(d) no clonogenic growth of post-**treatment** **tumor** cells indicates effectiveness of the bone marrow **treatment** technique.

US PAT NO: 5,672,603 [IMAGE AVAILABLE] L11:
23 of 105
SUMMARY:

BSUM(11)

Recently, **cancer** **treatment** with anti-Apo-I antibody has been attempted as an apoptosis-related therapy. Among the myelodysplastic syndrome (MDS), refractory anemia (RA) and refractory. . . be treated with a combination of retinoic acid or vitamin D3, which is a differentiation inducer for hemopoietic cells, and **GM**-*CSF** or IL-3 as an apoptosis regulating agent which suppresses excessive apoptosis of platelet producing cells whereas, in RAEB (refractory anemia. . .

US PAT NO: 5,672,493 [IMAGE AVAILABLE] L11:
24 of 105
SUMMARY:

BSUM(5)

Development . . . been applied to treatments using immunologic reagents and other substances derived from biologic sources to distinguish these from conventional surgical **treatment**, radiation therapy, and chemotherapy. Thus, immunologic approaches for the **treatment** of **cancer**, HIV/AIDS, and immune compromised patients, including infection/inflammatory conditions, are being actively pursued. For example, the development of cloned recombinant human gene products, including granulocyte-macrophage colony stimulating factor (**GM**-*CSF**), three species of interferon (IFN), interleukin-2 (IL-2), and **tumor** necrosis factor- α (TNF- α) has led to their testing in clinical trials, albeit with varying degrees of success (Lotze, M. T. . . on hematologic malignancies, including CML, hairy cell leukemia, non-Hodgkin's lymphoma, and cutaneous T-cell lymphoma, as well as administration of IL-2, **GM**-*CSF**, lymphokines-activated <-----User Break-----> parasitic infection, such as in acquired immune deficiency syndrome (AIDS).

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US PAT NO: 5,670,351 [IMAGE AVAILABLE] L11:
27 of 105
SUMMARY:

BSUM(18)

The . . . liters of peripheral blood would collect approximately 10.sup.5 CFU-GM although this number could be increased to 10.sup.6 CFU-GM by prior **treatment** of the donor with **GM**-*CSF*. Rapid recovery of a patient would require transfusion of approximately 1.times.10.sup.8 to 5.times.10.sup.8 CFU-GM which is 100 to 1,000 times. . . peripheral blood to increase the number of CFU-GM 2 to 3 orders of magnitude would significantly affect chemotherapy administration and **Cancer** **treatment**.

US PAT NO: 5,670,147 [IMAGE AVAILABLE] L11:
28 of 105
SUMMARY:

BSUM(18)

The . . . liters of peripheral blood would collect approximately 10.sup.5 CFU-GM although this number could be increased to 10.sup.6 CFU-GM by prior **treatment** of the donor with **GM**-*CSF*. Rapid recovery of a patient would require transfusion of approximately 1.times.10.sup.8 to 5.times.10.sup.8 CFU-GM which is 100 to 1,000 times. . . peripheral blood to increase the number of CFU-GM 2 to 3 orders of magnitude would significantly affect chemotherapy administration and **cancer** **treatment**.

US PAT NO: 5,662,896 [IMAGE AVAILABLE] L11:
29 of 105
SUMMARY:

BSUM(7)

Lymphokines have also been utilized in the **treatment** of **cancer**. Briefly, lymphokines are secreted by a variety of cells, and generally have an effect on specific cells in the generation. . . response. Examples of lymphokines include Interleukins (IL)-1, -2, -3, and -4, as well as colony stimulating factors such as G-CSF, **GM**-*CSF*, and M-CSF. Recently, one group has utilized IL-2 to stimulate peripheral blood cells in order to expand and produce large quantities of cells which are cytotoxic to **tumor** cells (Rosenberg et al., N. Engl. J. Med. 313:1485-1492, 1985).

US PAT NO: 5,658,912 [IMAGE AVAILABLE] L11:
30 of 105
SUMMARY:

BSUM(11)

Recently, **cancer** **treatment** with anti-Apo-I antibody has been attempted as an apoptosis-related therapy. Among the myelodysplastic syndrome (MDS), refractory anemia (RA) and refractory. . . be treated with a combination of retinoic acid or vitamin D.sub.3, which is a differentiation inducer for hemopoietic cells, and **GM**-*CSF* or IL-3 as an apoptosis regulating agent which suppresses excessive apoptosis of platelet producing cells whereas, in RAEB (refractory anemia. .

US PAT NO: 5,652,225 [IMAGE AVAILABLE] L11:
31 of 105
DETDESC:

DETD(3)

The . . . cells provides a therapeutic effect. The nucleic acid is selected based upon the desired therapeutic outcome. For example, in the **treatment** of ischemic diseases, one genetic material of choice would be a DNA encoding an angiogenic protein. DNA useful in the. . . DNA's of interest include those encoding hemoglobin, interleukin-1, interleukin-2, interleukin-3, interleukin-4, interleukin-4, interleukin-5, interleukin-6, interleukin-7, interleukin-8, interleukin-9, interleukin-10, interleukin-11, etc., **GM**-*CSF*, G-CSF, M-CSF, human growth factor, insulin, factor VIII, factor IX, tPA, LDL receptors, **tumor** necrosis factor, PDGF, EGF, NGF, IL-1ra, EPO, .beta.-globin and the like, as well as biologically active muteins of these proteins. . .

US PAT NO: 5,652,095 [IMAGE AVAILABLE] L11:
32 of 105
SUMMARY:

BSUM(9)

An . . . de novo AML and de novo acute lymphocytic leukemia (ALL), respectively (Van den Berghe et al., Nature 251: 437 (1974), **Cancer** Genet. Cytogenet. 17: 189-255 (1985); Fourth International Workshop on Chromosomes in Leukemia, (1982); Le Beau et al., J. Clin. Oncol. . . (1978); Golomb et al., Blood 60: 404-411 (1982)) or with previous exposure to alkylating agent chemotherapy or radiotherapy for the **treatment** of various malignancies (Le Beau et al., ibid. (1986)). A series of studies have revealed that the smallest commonly deleted. . . genes have been mapped to the 5q31 region, including the hematopoietic growth factors and interleukins IL-3, IL-4, IL-5, IL-9, and **GM**-*CSF*, and, the EGR-1 transcription factor (Huebner et al., Science 230: 1282-1285 (1985); Le Beau et al., Science 231: 984-987 (1986). . . at., Genomics 13: 803-808 (1992)). However, none of these genes currently appear to fulfill the requirements expected of a candidate **tumor** suppressor gene. Loss of one IL-3, IL-4, IL-5, and **GM**-*CSF* allele has been frequently, though not consistently, reported in leukemia and MDS patients with del(5q) (Le Beau et al., ibid. . . EGR-1 in del(5q) patients have yielded similar negative findings (G. Gilliland et al., Harvard University, personal communication). Thus, a candidate **tumor** suppressor gene remained to be identified in this region.

US PAT NO: 5,649,904 [IMAGE AVAILABLE] L11:
33 of 105
SUMMARY:

BSUM(5)

It is known that **GM**-*CSF* is a factor which is required for the survival, proliferation and differentiation of myeloid progenitor cells which are committed to. . . and macrophages (CFU-GMs). G-CSF similarly acts on myeloid progenitor cells committed to form mature granulocytes. Each is useful in the

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****treatment**** of myelo-suppression caused by
chemotherapeutic or irradiation ****treatment**** of ****cancer****.
Under such circumstances the HPSF is administered to a
patient, treated with chemo- or irradiation therapy, after the
re-infusion of. . . bone marrow) in order to stimulate the
proliferation and differentiation of the myeloid progenitor cells
found in the bone marrow. ****GM****-****CSF**** may also be
administered for 3-5 days before the removal of bone marrow
for later re-infusion.

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***Yellow Books: Corporate & Financial (File 81)
***Yellow Books: Law Firms (File 82)
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SYSTEM:HOME
Menu System II: D2 version 1.7.8 term=ASCII
*** DIALOG HOMEBASE(SM) Main Menu ***

Information:
1. Announcements (new files, reloads, etc.)
2. Database, Rates, & Command Descriptions
3. Help in Choosing Databases for Your Topic
4. Customer Services (telephone assistance, training,
seminars, etc.) 5. Product Descriptions

Connections:
6. DIALOG Menus(SM)
7. DIALOG Business Connection(R) and DIALOG
Headlines(SM) 8. DIALOG(R) Document Delivery
9. Data Star(R)
10. Other Online Menu Services & Files (MoneyCenter(R),
BNA, etc.)
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/H = Help /L = Logoff /NOMENU = Command
Mode

Enter an option number to view information or to connect to an
online service. Enter a BEGIN command plus a file number to
search a database (e.g., B1 for ERIC).
? b 410

06aug98 16:11:22 User217743 Session D451.1
\$0.00 0.149 DialUnits FileHomeBase
\$0.00 Estimated cost FileHomeBase
\$0.00 Estimated cost this search
\$0.00 Estimated total session cost 0.149 DialUnits
File 410:Chronolog(R) 1981-1998/Jul/Aug
(c) 1998 The Dialog Corporation plc

Set Items Description

? set hi %%%;set hi %%%

HILIGHT set on as '%%%'%%
%%HILIGHT set on as '%%%'
? b 411

06aug98 16:11:34 User217743 Session D451.2
\$0.00 0.107 DialUnits File410
\$0.00 Estimated cost File410
\$0.00 Estimated cost this search
\$0.00 Estimated total session cost 0.257 DialUnits File
411:DIALINDEX(R)

DIALINDEX(R)
(c) 1998 The Dialog Corporation plc

*** DIALINDEX search results display in an abbreviated ***
format unless you enter the SET DETAIL ON command. *** ?
set files biochem

>>> 162 is unauthorized
>>> 352 is unauthorized
>>>2 of the specified files are not available
You have 33 files in your file list.
(To see banners, use SHOW FILES command)
? s (mage)(3) and (gmcsf or gm)(csf)

Your SELECT statement is:
s (mage)(3) and (gmcsf or gm)(csf)

```

Items File
-----
4 5: BIOSIS PREVIEWS(R)_1969-1998/JUL W4
6 34: SciSearch(R) Cited Ref Sci_1990-1998/Jul W4
2 71: ELSEVIER BIOBASE_1994-1998/Aug W1
3 73: EMBASE_1974-1998/Aug W2
1 76: Life Sciences Collection_1982-1998/Jun
2 94: JICST-EPlus_1985-1998/May W4
1 144: Pascal_1973-1998/Jul
2 155: MEDLINE(R)_1966-1998/Sep W4
1 351: DERWENT
WPI_1963-1998/UD=9830;UP=9827;UM=9825 1
377: Derwent Drug File_1983-1998/Jul W4 1 399:
CA SEARCH(R)_1967-1998/UD=12905

```

11 files have one or more items; file list includes 33 files.
? rf

Your last SELECT statement was:
S (MAGE(3) AND (GMCSF OR GM())CSF)

```

Ref Items File
-----
N1 6 34: SciSearch(R) Cited Ref Sci_1990-1998/Jul
W4 N2 4 5: BIOSIS
PREVIEWS(R)_1969-1998/JUL W4 N3 3 73:
EMBASE_1974-1998/Aug W2
N4 2 71: ELSEVIER BIOBASE_1994-1998/Aug W1
N5 2 94: JICST-EPlus_1985-1998/May W4
N6 2 155: MEDLINE(R)_1966-1998/Sep W4
N7 1 76: Life Sciences Collection_1982-1998/Jun N8
1 144: Pascal_1973-1998/Jul
N9 1 351: DERWENT
WPI_1963-1998/UD=9830;UP=9827;UM=9825 N10 1
377: Derwent Drug File_1983-1998/Jul W4 11 files have one
or more items; file list includes 33 files.
- Enter P or PAGE for more -
? b 155

```

06aug98 16:13:29 User217743 Session D451.3
\$2.00 2.000 DialUnits File411
\$2.00 Estimated cost File411
\$2.00 Estimated cost this search
\$2.00 Estimated total session cost 2.257 DialUnits
File 155:MEDLINE(R) 1966-1998/Sep W4
(c) format only 1998 Dialog Corporation

```

Set Items Description
-----
? s (mage(3) and (gmcsf or gm())csf)

248 MAGE
1563270 3
86 MAGE(W)3
85 GMCSF
19677 GM
31490 CSF
6565 GM(W)CSF
S1 2 (MAGE(3) AND (GMCSF OR GM())CSF)
? t s1/3,ab/1,2

```

1/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1998 Dialog Corporation. All rts. reserv.

09292446 97477808
Transfection of IL-2 augments CTL response to human melanoma cells in vitro: immunological characterization of a

melanoma vaccine. van Elsas A; Aarnoudse C; van der Minne CE; van der Spek CW; Brouwenstijn N; Osanto S; Schrier PI
Department of Clinical Oncology, University Hospital Leiden, The Netherlands.

J Immunother (UNITED STATES) Sep 1997, 20 (5)
p343-53, ISSN 1053-8550 Journal Code: CUQ
Languages: ENGLISH

Document type: JOURNAL ARTICLE

We have transfected human melanoma cell line 518A2 with the cDNA encoding interleukin-2 (IL-2) or granulocyte-macrophage colony-stimulating factor (%%%GM%%-%%%CSF%%), and compared cytokine-producing clones for their ability to induce melanoma-specific cytotoxic T lymphocytes (CTL) from autologous peripheral blood mononuclear cells (PBMC) in vitro. The parental cell line expressed HLA-A1, HLA-A2, ICAM-1, LFA-3, in addition to the common CTL antigens MAGE-1, %%%MAGE%%-%%%3%%, tyrosinase, gp100, and Melan-A/MART-1. Stimulation of autologous PBMC responders with the IL-2-transfected clone 518/IL2.14 specifically induced CTL lines reactive with all cell lines derived from the autologous patient. Strikingly, %%%GM%%-%%%CSF%%-transfected 518A2 cells did not induce anti-tumor CTL reactivity. CTL induction against 518/IL2.14 was independent of HLA class II expression or CD4 help. The parental cell line 518A2 gained immunogenic properties when high concentrations of IL-2 were supplied exogenously, indicating that IL-2 produced and present at high levels locally by itself enhanced immunogenicity. From the autologous CTL line reactive with 518/IL2.14, clones were generated against an as yet unknown antigen, which was present in all autologous melanoma cell lines as well as in 7 of 15 HLA-A2+ melanoma cell lines tested, but not in melanocytes. These results will be discussed with respect to the possibility of using IL-2-transfected melanoma cells as a vaccine for treatment of patients with melanoma.

1/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
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08881361 97053992
Induction of antigen-specific tumor immunity by genetic and cellular vaccines against MAGE: enhanced tumor protection by coexpression of granulocyte-macrophage colony-stimulating factor and B7-1. Bueler H; Mulligan RC
Howard Hughes Medical Institute, Children's Hospital, Boston, Massachusetts, USA.
Mol Med (UNITED STATES) Sep 1996, 2 (5) p545-55, ISSN 1076-1551 Journal Code: CG3
Contract/Grant No.: CA63399, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND: A number of tumors express antigens that are recognized by specific cytotoxic T cells. The normal host immune responses, however, are not usually sufficient to cause tumor rejection. Using appropriate immunization strategies, tumor-specific antigens may serve as targets against which tumor-destructive immune responses can be generated. MAGE-1 and %%%MAGE%%-%%%3%% are two clinically relevant antigens expressed in many human melanomas and other tumors, but not in normal tissues, except testis. Here, we have investigated whether DNA and cellular vaccines against MAGE-1 and %%%MAGE%%-%%%3%% can induce antigen-specific anti-tumor immunity and cause rejection of MAGE-expressing tumors. MATERIALS AND METHODS: Mice were immunized against MAGE-1 and

late, but get.

%%MAGE%%-%%3%% by subcutaneous injection of genetically modified embryonic fibroblasts or intramuscular injection of purified DNA. Mice were injected with lethal doses of B16 melanoma cells expressing the corresponding MAGE antigens or the unrelated protein SIV tat, and tumor development and survival were monitored. RESULTS: Intramuscular expression of MAGE-1 and %%MAGE%%-%%3%% by plasmid DNA injection and subcutaneous immunization with syngeneic mouse embryonic fibroblasts transduced with recombinant retroviruses to express these antigens induced specific immunity against tumors expressing MAGE-1 and %%MAGE%%-%%3%%. Both CD4+ and CD8+ T cells were required for anti-tumor immunity. Coexpression of granulocyte-macrophage colony-stimulating factor (%%GM%%-%%CSF%%) or B7-1 significantly increased anti-tumor immunity in an antigen-specific manner and resulted in a considerable proportion of mice surviving lethal tumor challenge. CONCLUSIONS: Our results suggest that genetic and cellular vaccines against MAGE and other tumor antigens may be useful for the therapy of tumors expressing specific markers, and that %%GM%%-%%CSF%% and B7-1 are potent stimulators for the induction of antigen-specific tumor immunity.

? s (gmcsf or gm())csf)

85 GMCSF

19677 GM

31490 CSF

6565 GM(W)CSF

S2 6643 (GMCSF OR GM())CSF)

? s s2 and fusion()protein

6643 S2

63265 FUSION

744852 PROTEIN

7988 FUSION(W)PROTEIN

S3 86 S2 AND FUSION()PROTEIN

? s (gmcsf or gm())csf)(p)(anchor or membrane())attach? or transmembrane)

>>>Invalid syntax

? s (gmcsf or gm())csf)(5np)(anchor or membrane())attach? or transmembrane)

>>>Invalid syntax

? s (gmcsf or gm())csf)(5n)(anchor or membrane())attach? or transmembrane)

85 GMCSF

19677 GM

31490 CSF

6565 GM(W)CSF

3886 ANCHOR

405145 MEMBRANE

59019 ATTACH?

478 MEMBRANE(W)ATTACH?

22672 TRANSMEMBRANE

S4 4 (GMCSF OR GM())CSF)(5N)(ANCHOR OR MEMBRANE())ATTACH? OR TRANSMEMBRANE)

? t s4/3,ab/all

4/3,AB/1

DIALOG(R)File 155:MEDLINE(R)

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09047532 97266587

Oligomerization of the soluble granulocyte-macrophage colony-stimulating factor receptor: identification of the

functional ligand-binding species. Brown CB; Pihl CE; Murray EW

Department of Medicine, The University of Calgary, Alberta, Canada. cbrown@acs.ucalgary.ca

Cytokine (UNITED STATES) Apr 1997, 9 (4) p219-25, ISSN 1043-4666 Journal Code: A52

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The ligand-specific alpha subunit of the dimeric human %%GM%%-%%CSF%% receptor exists in both %%transmembrane%% anchored (tmGM-CSFR alpha) and soluble (sGM-CSFR alpha) isoforms. sGM-CSFR alpha binds to GM-CSF in solution and antagonizes GM-CSF biological activity in vitro. In an effort to better understand the biological properties of sGM-CSFR alpha the authors have attempted to define the exact stoichiometry of the interaction between GM-CSF and sGM-CSFR alpha. Size separation of sGM-CSFR alpha by polyacrylamide gel electrophoresis (PAGE) under non-reducing conditions demonstrated that sGM-CSFR alpha can exist in solution not only in a monomeric state but also in higher order oligomers. FPLC analysis of ligand/sGM-CSFR alpha complexes suggested that only one of these sGM-CSFR alpha species could functionally bind GM-CSF. PAGE analysis of FPLC fractions demonstrated that the peak of GM-CSF binding activity corresponded to the presence of a monomeric form of sGM-CSFR alpha. The experiments demonstrate that while sGM-CSFR alpha can adopt oligomeric forms in solution, the binding of GM-CSF to sGM-CSFR alpha most likely occurs in a (GM-CSF)1 (sGM-CSFR alpha)1 configuration.

4/3,AB/2

DIALOG(R)File 155:MEDLINE(R)

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08622251 96279041

Ligand-independent cell surface expression of the human soluble granulocyte-macrophage colony-stimulating factor receptor alpha subunit depends on co-expression of the membrane-associated receptor beta subunit. Murray EW; Pihl C; Morcos A; Brown CB

Department of Medicine, Cancer Biology Research Group, The University of Calgary, Calgary, Alberta, T2N 4N1 Canada. J Biol Chem (UNITED STATES) Jun 28 1996, 271 (26) p15330-5, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The hematopoietic cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) mediates its activity through binding to cell surface receptors. The receptor for GM-CSF belongs to a superfamily of cytokine receptors characterized by a conserved extracellular motif. The high affinity %%GM%%-%%CSF%% receptor (GMR) consists of two %%transmembrane%% anchored subunits; a ligand binding alpha subunit (transmembrane GMRalpha) and a signal transducing beta subunit (GMRbeta), both of which belong to the cytokine receptor superfamily. The human GM-CSF receptor alpha subunit also exists in a soluble form (solGMRalpha), which antagonizes GM-CSF activity in vitro. We directly tested the potential for solGMRalpha to interact with GMRbeta in vitro. Our experiments demonstrated that exogenous solGMRalpha, even in the presence of GM-CSF, does not interact with GMRbeta on the cell surface. However, when solGMRalpha and GMRbeta are co-expressed in baby hamster kidney cells, solGMRalpha is retained on the cell surface and forms a functional intermediate affinity GM-CSF binding complex

(Kd = 331 pM). In addition, the cell surface expression of solGMRalpha is independent of the presence of GM-CSF as demonstrated using flow cytometry. Cells expressing only solGMRalpha do not show cell surface retention or form functional GM-CSF cell surface binding complexes. Sequencing of our GMRbeta clone revealed a nucleotide substitution (A --> C) resulting in the substitution of Ala for Glu at position 9 from the amino terminus of the mature GMRbeta peptide. Because the GMRbeta (A --> C) clone is capable of forming functional high affinity receptors with transmembrane GMRalpha (Kd = 64 pM), we feel that the cell surface retention of solGMRalpha is independent of the GMRbeta mutation. We suggest that the co-expression and interaction of solGMRalpha and GMRbeta represents a previously unrecognized GM-CSF receptor complex and a novel, ligand-independent mechanism of cytokine receptor assembly.

4/3,AB/3

DIALOG(R)File 155:MEDLINE(R)

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08267455 95195214

In vitro characterization of the human recombinant soluble granulocyte-macrophage colony-stimulating factor receptor. Brown CB; Beaudry P; Laing TD; Shoemaker S; Kaushansky K Department of Medicine, University of Calgary, Alberta, Canada. Blood (UNITED STATES) Mar 15 1995, 85 (6) p1488-95, ISSN 0006-4971 Journal Code: A8G Contract/Grant No.: CA31615, CA, NCI Languages: ENGLISH

Document type: JOURNAL ARTICLE

We have cloned, expressed, and partially purified a naturally occurring, truncated, soluble form of the human granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor alpha subunit to investigate its biochemical and biologic properties. The soluble receptor species lacks the transmembrane and cytoplasmic domains that are presumably removed from the intact receptor cDNA by a mechanism of alternative splicing. The resulting soluble 55- to 60-kD glycosylated receptor species binds GM-CSF with a dissociation constant (kd) of 3.8 nmol/L. The soluble GM-CSF receptor successfully competes for %%%GM%%-%%%CSF%%-% binding not only with the %%%transmembrane%%-%-anchored %%%GM%%-%-%%%CSF%%-% receptor alpha subunit but also with the native oligomeric high-affinity receptor complex. In addition, in human bone marrow colony-forming assays, the soluble GM-CSF receptor species can antagonize the activity of GM-CSF. Our data suggest that the soluble GM-CSF receptor may be capable of acting in vivo as a modulator of the biologic activity of GM-CSF.

4/3,AB/4

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

06628070 90217679

%%GM%%-%%%CSF%%-%: receptor structure and %%%transmembrane%%-% signaling. DiPersio JF; Golde DW; Gasson JD

Department of Medicine, UCLA Medical Center 90024.

Int J Cell Cloning (UNITED STATES) Jan 1990, 8

Suppl 1 p63-74; discussion 74-5, ISSN 0737-1454 Journal Code: IJC

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Human granulocyte-macrophage colony-stimulating factor

(GM-CSF) both stimulates hematopoietic precursor cells to grow as well as enhances the function of mature effector cells, such as neutrophils, eosinophils and macrophages. All of the biological actions of GM-CSF appear to be mediated via binding to a single class of high-affinity receptors present on all responsive cells. Affinity cross-linking experiments demonstrate that the same 98 kDa cross-linked species seen on other GM-CSF-responsive cells is also detected on a choriocarcinoma cell line, JAR. However, JAR cells express significantly increased numbers (10,000 sites/cell) of low-affinity (Kd approximately 1.5 nM) GM receptors. The GM-CSF receptor is a glycoprotein which binds to wheat germ agglutinin-sepharose. It is dramatically downregulated on neutrophils by phorbol esters and formyl-methionyl-leucine-phenylalanine (fMLP), but not by phosphatidylinositol-dependent phospholipase C. GM-CSF primes neutrophils for enhanced response to secondary stimuli, such as ionophore and chemotactic factors. Specifically, GM-CSF enhances 3H-arachidonic acid release, synthesis of leukotriene B4 and platelet activity factor in response to fMLP and the calcium ionophores. ? ds

Set Items Description

S1 2 (MAGE()3) AND (GMCSF OR GM()CSF)

S2 6643 (GMCSF OR GM()CSF)

S3 86 S2 AND FUSION()PROTEIN

S4 4 (GMCSF OR GM()CSF)(5N)(ANCHOR OR MEMBRANE()ATTACH? OR TRAN- S MEMBRANE) ? s s3 not s4

86 S3

4 S4

S5 86 S3 NOT S4

? s s5 and anchor?

86 S5

13836 ANCHOR?

S6 0 S5 AND ANCHOR?

? t s5/6/1-10

5/6/1

09580459 98256771

A recombinant fragment of Helicobacter pylori CagA affects proliferation of human cells.

5/6/2

09528831 98254101

In vivo targeting of leukemic cells using diphtheria toxin fused to murine %%%GM%%-%%%CSF%%-%.

5/6/3

09478545 98184878

Construction and binding kinetics of a soluble granulocyte-macrophage colony-stimulating factor receptor alpha-chain-Fc %%%fusion%%-%%%protein%%-%.

5/6/4

09445870 98149700

Characterization of the microheterogeneities of PIXY321, a genetically engineered granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%%-%%%protein%%-% expressed in yeast.

5/6/5

09427488 98119703

Interleukin-6 receptor-interleukin-6 fusion proteins with enhanced interleukin-6 type pleiotropic activities.

5/6/6

09316912 97465475

Sensitivity of human acute myeloid leukaemia to diphtheria toxin-%%GM%%-%%CSF%% %%fusion%% %%protein%%.

5/6/7

09288796 98017594

Neutrophil maturation of CD34+ cells from peripheral blood and bone marrow in serum-free culture medium with PIXY321 and granulocyte-colony stimulating factor (G-CSF).

5/6/8

09286001 98008131

Modulation of the apoptotic response of human myeloid leukemia cells to a diphtheria toxin granulocyte-macrophage colony-stimulating factor %%fusion%% %%protein%%.

5/6/9

09273184 97336614

Granulocyte-macrophage colony-stimulating factor/interleukin-3 %%fusion%% %%protein%% versus granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for non-Hodgkin's lymphoma: results of a randomized double-blind trial.

5/6/10

09258988 97169053

Thrombospondin, a negative modulator of megakaryocytopoiesis. ? t s5/6/11-20

5/6/11

09249112 97051758

Human eosinophils express functional CD30 ligand and stimulate proliferation of a Hodgkin's disease cell line.

5/6/12

09237298 96343853

Differential expression of Fas (CD95) and Fas ligand on normal human phagocytes: implications for the regulation of apoptosis in neutrophils.

5/6/13

09227691 96223410

Phase I/II trial of PIXY321 to enhance engraftment following autologous bone marrow transplantation for lymphoid malignancy.

5/6/14

09225646 96200424

The effect of the %%GM%%-%%CSF%%/IL-3 %%fusion%% %%protein%% PIXY321 on bone marrow and circulating haemopoietic cells of previously untreated patients with cancer.

5/6/15

09205372 95355467

Signal transduction by a CD16/CD7/Jak2 %%fusion%% %%protein%%.

5/6/16

09178049 97449096

New understanding of the pathogenesis of CML: a prototype of early neoplasia.

5/6/17

09172020 97447239

Ricin fusion toxin targeted to the human granulocyte-macrophage colony stimulating factor receptor is selectively toxic to acute myeloid leukemia cells.

5/6/18

09163493 97387249

A recombinant %%GM%%-%%CSF%%-PE40 ligand toxin is functionally active but not cytotoxic to cells.

5/6/19

09101143 97353148

The signal transduction through Grb2/Ash in hematopoietic cells.

5/6/20

09042986 97284702

The kinase domain of Jak2 mediates induction of bcl-2 and delays cell death in hematopoietic cells.
? ds

Set Items Description

S1 2 (MAGE()3) AND (GMCSF OR GM()CSF)

S2 6643 (GMCSF OR GM()CSF)

S3 86 S2 AND FUSION()PROTEIN

S4 4 (GMCSF OR GM()CSF)(5N)(ANCHOR OR

MEMBRANE()ATTACH? OR TRAN- S MEMBRANE)

S5 86 S3 NOT S4

S6 0 S5 AND ANCHOR?

? t s5/6/21-86

5/6/21

09040316 97246188

In vitro production of megakaryocytes from PIXY321 versus %%GM%%-%%CSF%%-mobilized peripheral blood progenitor cells.

5/6/22

09032817 96430277

C-kit ligand (SCF) in human multiple myeloma cells.

5/6/23

09007780 97261978

Purification and molecular cloning of SH2- and SH3-containing inositol polyphosphate-5-phosphatase, which is involved in the signaling pathway of granulocyte-macrophage colony-stimulating factor, erythropoietin, and Bcr-Abl.

5/6/24

08938349 97199402

The conserved lymphokine element-0 in the IL5 promoter binds to a high mobility group-1 protein.

5/6/25

08853869 97113340

A nine-amino acid peptide from IL-1beta augments antitumor immune responses induced by protein and DNA vaccines.

5/6/26

08843470 97102692

Regulation of the synthesis of bcl-2 protein by growth factors.

5/6/27

08782302 97054671

Exogenous and endogenous antigens are differentially presented by mast cells to CD4+ T lymphocytes.

5/6/28

08747851 96420633

Phase I trial of recombinant %%%fusion%% protein PIXY321 for mobilization of peripheral-blood cells.

5/6/29

08717835 96071135

PIXY321 protects against Ara-C or taxol-induced apoptosis and loss of clonogenic survival of normal human bone marrow progenitor cells.

5/6/30

08693902 96376358

DNA immunization induces protective immunity against B-cell lymphoma.

5/6/31

08682066 96351963

Interleukins and colony stimulating factors in human myeloid leukemia cell lines.

5/6/32

08640391 96309626

Mechanism of transcriptional activation of the immediate early gene Egr-1 in response to PIXY321.

5/6/33

08596055 96247489

A phase II study of cyclophosphamide followed by PIXY321 as a means of mobilizing peripheral blood hematopoietic progenitor cells [published erratum appears in Exp Hematol 1997 Mar;25(3):270]

5/6/34

08581763 96203784

Prospective, randomized trial of 5-fluorouracil, leucovorin, doxorubicin, and cyclophosphamide chemotherapy in combination with the interleukin-3/granulocyte-macrophage colony-stimulating factor (%%GM%%-%%CSF%%) %%%fusion%% %%%protein%% (PIXY321) versus %%%GM%%-%%CSF%% in patients with advanced breast cancer.

5/6/35

08571801 96200992

Expression of FLT3 receptor and response to FLT3 ligand by leukemic cells.

5/6/36

08569734 96194723

Early suppressive effects of chemotherapy and cytokine treatment on committed versus primitive haemopoietic progenitors in patient bone marrow.

5/6/37

08509016 96132719

The AML1/ETO %%%fusion%% %%%protein%% blocks transactivation of the %%%GM%%-%%CSF%% promoter by AML1B.

5/6/38

08507116 96130277

Immunocytochemical analysis of tumor cells in pre- and post-culture peripheral blood progenitor cell collections from breast cancer patients.

5/6/39

08494343 96116885

Cytofluorimetric and functional analysis of c-kit receptor in acute leukemia.

5/6/40

08434579 96033074

Characteristic biological features of human megakaryoblastic leukaemia cell lines.

5/6/41

08418176 95385746

Flt3 ligand stimulates/costimulates the growth of myeloid stem/progenitor cells.

5/6/42

08412834 95256249

The proto-oncogene product c-Cbl becomes tyrosine phosphorylated by stimulation with %%%GM%%-%%CSF%% or Epo and constitutively binds to the SH3 domain of Grb2/Ash in human hematopoietic cells.

5/6/43

08411657 95222300

Clinical applications of hematopoietic growth factors [see comments]

5/6/44

08409792 95137005

Tyrosine phosphorylation of p95Vav in myeloid cells is regulated by %%%GM%%-%%CSF%%, IL-3 and steel factor and is constitutively increased by p210BCR/ABL [see comments]

5/6/45

08402600 95399776

A murine cytokine fusion toxin specifically targeting the murine granulocyte-macrophage colony-stimulating factor

(%GM%-CSF) receptor on normal committed bone marrow progenitor cells and %GM%-CSF-dependent tumor cells.

5/6/46

08393555 95387656

The acute promyelocytic leukemia-specific PML/RAR alpha %fusion% %protein% reduces the frequency of commitment to apoptosis upon growth factor deprivation of %GM%-CSF-dependent myeloid cells.

5/6/47

08324176 95293979

The amino-terminal portion of the JAK2 protein kinase is necessary for binding and phosphorylation of the granulocyte-macrophage colony-stimulating factor receptor beta c chain.

5/6/48

08271043 95204905

Induction of autoantibody responses to %GM%-CSF by hyperimmunization with an Id-%GM%-CSF %fusion% %protein%.

5/6/49

08270412 95203343

Effects of in vivo treatment with PIXY321 (%GM%-CSF/IL-3 %fusion% %protein%) on proliferation kinetics of bone marrow and blood myeloid progenitor cells in patients with sarcoma.

5/6/50

08242730 95268047

Primitive hematopoietic progenitor cells are present in peripheral blood autografts.

5/6/51

08228241 94374493

Characterization and quantitation of primitive hematopoietic progenitor cells present in peripheral blood autografts.

5/6/52

08187179 95268058

Cytokine-dependent ex vivo expansion of early subsets of CD34+ cord blood myeloid progenitors is enhanced by cord blood plasma, but expansion of the more mature subsets of progenitors is favored.

5/6/53

08186468 95210988

Granulocyte-colony stimulating factor, granulocyte-macrophage colony stimulating factor, PIXY-321, stem cell factor, interleukin-3, and interleukin-7: receptor binding and effects on clonogenic proliferation in acute lymphoblastic leukemia.

5/6/54

08186050 95195626

Enrichment of peripheral blood stem cells in a primate model following administration of a single dose of rh-IL-1 beta.

5/6/55

08183739 95118872

Expression and functional role of c-kit ligand (SCF) in human multiple myeloma cells.

5/6/56

08182496 95086205

Regulation of interleukin-11 protein and mRNA expression in neonatal and adult fibroblasts and endothelial cells.

5/6/57

08180995 95052644

Idiotypic-cytokine fusion proteins as cancer vaccines. Relative efficacy of IL-2, IL-4, and granulocyte-macrophage colony-stimulating factor.

5/6/58

08174357 94289726

Expression of interleukin-1 beta gene in candidate human hematopoietic stem cells.

5/6/59

08172146 94238907

Mast cell growth factor (c-kit ligand) restores growth of multipotent progenitors in myelodysplastic syndrome.

5/6/60

08171352 94220683

Thy-1 expression is linked to functional properties of primitive hematopoietic progenitor cells from human umbilical cord blood.

5/6/61

08133699 95180241

Potential role of granulocyte-macrophage colony-stimulating factor as vaccine adjuvant.

5/6/62

08109035 95135335

Expression of a biologically active human granulocyte-macrophage colony stimulating factor %fusion% %protein% in Escherichia coli.

5/6/63

07990666 94355911

PIXY321 (%GM%-CSF/IL-3 %fusion% %protein%): biology and early clinical development.

5/6/64

07889300 94201787

Effects of PIXY321, a granulocyte-macrophage colony-stimulating factor/interleukin-3 %fusion% %protein%, on chemotherapy-induced multilineage myelosuppression in patients with sarcoma.

5/6/65

07812523 93244623

Effect of hemopoietic growth factors G-CSF and pIXY 321 on the activity of high dose Ara-C in human myeloid leukemia cells.

5/6/66
07806268 94154609
c-kit ligand augments granulocyte-macrophage colony growth from patients with 5q- syndrome.

5/6/67
07803969 94083894
Cytotoxicity of a recombinant diphtheria toxin-granulocyte colony-stimulating factor %%%fusion%% %%%protein%% on human leukemic blast cells.

5/6/68
07800297 94009450
Increase in peripheral blood megakaryocyte progenitors following cancer therapy with high-dose cyclophosphamide and hematopoietic growth factors.

5/6/69
07796045 93307458
Modulation of the activity of a human granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%% %%%protein%% (pIXY 321) by the macrocyclic lactone protein kinase C activator bryostatin 1.

5/6/70
07794965 93283672
Cytokine-induced selective expansion and maturation of erythroid versus myeloid progenitors from purified cord blood precursor cells.

5/6/71
07747966 94191166
Modulation by bryostatin 1 of the in vitro radioprotective effects of the %%%GM%%-%%%CSF%%/IL-3 %%%fusion%% %%%protein%%, PIXY 321, on normal human myeloid progenitors.

5/6/72
07712747 94107629
Retinoid receptors and acute promyelocytic leukaemia.

5/6/73
07644237 94009432
The effects of treatment with PIXY321 (%%GM%%-%CSF%%/IL-3 %%%fusion%% %%%protein%%) on human polymorphonuclear leukocyte function.

5/6/74
07637902 94000569
PIXY 321 (%%GM%%-%CSF%%/IL-3 %%%fusion%% %%%protein%%).

5/6/75
07618238 93386061
A %%%GM%%-%CSF%%/IL-3 %%%fusion%% %%%protein%% promotes neutrophil and platelet recovery in sublethally irradiated rhesus monkeys.

5/6/76
07520431 93226047
Idiotypic/granulocyte-macrophage colony-stimulating factor %%%fusion%% %%%protein%% as a vaccine for B-cell lymphoma [see comments]

5/6/77
07387193 93081792
Granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%% %%%protein%% (pIXY 321) enhances high-dose Ara-C-induced programmed cell death or apoptosis in human myeloid leukemia cells.

5/6/78
07340860 92324291
GMP-140 (P-selectin/CD62) binds to chronically stimulated but not resting CD4+ T lymphocytes and regulates their production of proinflammatory cytokines.

5/6/79
07338373 92267123
Ex vivo expansion of peripheral blood progenitor cells with recombinant cytokines.

5/6/80
07337089 92233922
Recombinant %%%GM%%-%CSF%%/IL-3 %%%fusion%% %%%protein%% : its effect on in vitro human megakaryocytopoiesis.

5/6/81
07334503 92119283
Role of c-kit ligand in the expansion of human hematopoietic progenitor cells.

5/6/82
07002795 91311304
CD45 cell surface antigens are linked to stimulation of early human myeloid progenitor cells by interleukin 3 (IL-3), granulocyte/macrophage colony-stimulating factor (%%GM%%-%CSF%%), a %%%GM%%-%CSF%%/IL-3 %%%fusion%% %%%protein%%, and mast cell growth factor (a c-kit ligand).

5/6/83
06923839 91288552
Enhanced hematopoietic activity of a human granulocyte/macrophage colony-stimulating factor-interleukin 3 %%%fusion%% %%%protein%%.

5/6/84
06870494 92121667
Hybrid cytokines as hematopoietic growth factors.

5/6/85
06692943 91199046
Hematopoietic effects of a granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%% %%%protein%%.

5/6/86
06224722 89193299
E. coli derived human granulocyte-macrophage colony-stimulating factor (rh %%%GM%%-%CSF%%) available for clinical trials.
? t s5/6/1-10t s5/3,ab/57

>>>'10T' not recognized as item list
? t s5/3,ab/57

5/3,AB/57
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1998 Dialog Corporation. All rts. reserv.

08180995 95052644

Idiotypic-cytokine fusion proteins as cancer vaccines.
Relative efficacy of IL-2, IL-4, and granulocyte-macrophage
colony-stimulating factor. Chen TT; Tao MH; Levy R
Department of Medicine, School of Medicine, Stanford
University, CA 94305.

J Immunol (UNITED STATES) Nov 15 1994, 153 (10)
p4775-87, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: CA33399, CA, NCi; GM07365, GM,
NIGMS Languages: ENGLISH

Document type: JOURNAL ARTICLE

Idiotypic determinants, antigenic sites expressed on the
variable region of Ig molecules of malignant B cells, represent
tumor-specific Ags but are weak immunogens. We have
previously shown that the immunogenicity can be dramatically
increased by fusing tumor Id to granulocyte macrophage (GM-CSF). Here, we demonstrate that
fusion proteins with IL-2 or IL-4 can also be highly
immunogenic. Co-immunization of these fusion proteins with
another Id demonstrated the importance of physical linkage
between the cytokine and relevant Ag for this enhancement. All
three fusion proteins are capable of eliciting significant
levels of specific Abs against the Id without the use of carrier
proteins or adjuvants, although the
fusion protein appeared to be unique in its ability to
induce higher titers of anti-Id Abs in the primary response.
Furthermore, the Id-IL-2 fusion protein induced high titers of IgG2a and IgG3 anti-Id Abs, whereas
the Id-IL-4 and Id-GM-CSF fusion
proteins did not. Despite the differences, tumor protection
was comparable in all mice having significant titers of anti-Id
Abs, regardless of the fusion protein used. We concluded that Id-cytokine fusion proteins are
potent immunogens that can elicit significant antitumor
immunity. The general approach of fusing a cytokine to a
potential Ag may be applicable to the design of vaccines for
immunotherapy of other types of tumors as well as for other
pathogens and disease states.

? b 5

06aug98 16:24:59 User217743 Session D451.4

\$6.00 2.000 DialUnits File155

\$0.00 86 Type(s) in Format 6

\$1.40 7 Type(s) in Format 4 (UDF)

\$1.40 93 Types

\$7.40 Estimated cost File155

\$7.40 Estimated cost this search

\$9.40 Estimated total session cost 4.257 DialUnits

File 5:BIOSIS PREVIEWS(R) 1969-1998/JUL W4

(c) 1998 BIOSIS

Set Items Description

? s (gmcsf or gm(cs)f)(5n)(anchor or membrane)(attach? or
transmembrane)

295 GMCSF

20946 GM

32963 CSF

7575 GM(W)CSF

4324 ANCHOR

409735 MEMBRANE

63441 ATTACH?

651 MEMBRANE(W)ATTACH?

26273 TRANSMEMBRANE
S1 6 (GMCSF OR GM(CSF))(5N)(ANCHOR OR
MEMBRANE)(ATTACH? OR
TRANSMEMBRANE)
? t s1/3,ab/all

1/3,AB/1

DIALOG(R)File 5:BIOSIS PREVIEWS(R)

(c) 1998 BIOSIS. All rts. reserv.

13547296 BIOSIS Number: 99547296

Oligomerization of the soluble granulocyte-macrophage
colony-stimulating factor receptor: Identification of the
functional ligand-binding species Brown C B; Pihl C E;
Murray E W

Room 2880, Health Sci. Center, Univ. Calgary, 3330 Hosp.
Drive N.W. Calgary, AB T2N 4N1, Canada

Cytokine 9 (4). 1997. 219-225.

Full Journal Title: Cytokine

ISSN: 1043-4666

Language: ENGLISH

Print Number: Biological Abstracts Vol. 103 Iss. 012 Ref.

170724 The ligand-specific alpha subunit of the dimeric
human GM-CSF receptor exists in
both transmembrane anchored
(tmGM-CSFR-alpha) and soluble (sGM-CSFR-alpha)
isoforms. sGM-CSFR-alpha binds to GM-CSF in solution
and antagonizes GM-CSF biological activity in vitro. In an effort
to better understand the biological properties of
sGM-CSFR-alpha the authors have attempted to define the
exact stoichiometry of the interaction between GM-CSF and
sGM-CSFR-alpha. Size separation of sGM-CSFR-alpha by
polyacrylamide gel electrophoresis (PAGE) under
non-reducing conditions demonstrated that sGM-CSFR-alpha
can exist in solution not only in a monomeric state but also
in higher order oligomers. FPLC analysis of
ligand/sGM-CSFR-alpha complexes suggested that only
one of these sGM-CSFR-alpha species could functionally
bind GM-CSF. PAGE analysis of FPLC fractions
demonstrated that the peak of GM-CSF binding activity
corresponded to the presence of a monomeric form of
sGM-CSFR-alpha. The experiments demonstrate that while
sGM-CSFR-alpha can adopt oligomeric forms in solution,
the binding of GM-CSF to sGM-CSFR-alpha most likely
occurs in a (GM-CSF)-1 (sGM-CSFR-alpha)-1 configuration.

1/3,AB/2

DIALOG(R)File 5:BIOSIS PREVIEWS(R)

(c) 1998 BIOSIS. All rts. reserv.

13084059 BIOSIS Number: 99084059

Ligand-independent cell surface expression of the human
soluble granulocyte-macrophage colony-stimulating factor
receptor alpha subunit depends on co-expression of the
membrane-associated receptor beta subunit Murray E W; Pihl
C; Morcos A; Brown C B

Dep. Med., Health Sci. Cent., 3330 Hospital Dr. NW., Univ.
Calgary, Calgary, AB T2N 4N1, Canada

Journal of Biological Chemistry 271 (26). 1996.

15330-15335. Full Journal Title: Journal of Biological
Chemistry

ISSN: 0021-9258

Language: ENGLISH

Print Number: Biological Abstracts Vol. 102 Iss. 004 Ref.

049508 The hematopoietic cytokine
granulocyte-macrophage colony-stimulating factor (GM-CSF)
mediates its activity through binding to cell surface

receptors. The receptor for GM-CSF belongs to a superfamily of cytokine receptors characterized by a conserved extracellular motif. The high affinity %%%GM%%-%%%CSF%% receptor (GMR) consists of two %%%transmembrane%% anchored subunits; a ligand binding a subunit (transmembrane GMR-alpha) and a signal transducing beta subunit (GMR-beta), both of which belong to the cytokine receptor superfamily. The human GM-CSF receptor a subunit also exists in a soluble form (solGMR-alpha), which antagonizes GM-CSF activity in vitro. We directly tested the potential for solGMR-alpha to interact with GMR-beta in vitro. Our experiments demonstrated that exogenous solGMR-alpha, even in the presence of GM-CSF, does not interact with GMR-beta on the cell surface. However, when solGMR-alpha and GMR-beta are co-expressed in baby hamster kidney cells, solGMR-alpha is retained on the cell surface and forms a functional intermediate affinity GM-CSF binding complex (K-d = 331 pM). In addition, the cell surface expression of solGMR-alpha is independent of the presence of GM-CSF as demonstrated using flow cytometry. Cells expressing only solGMR-alpha do not show cell surface retention or form functional GM-CSF cell surface binding complexes. Sequencing of our GMR-beta clone revealed a nucleotide substitution (A fwdarw C) resulting in the substitution of Ala for Glu at position 9 from the amino terminus of the mature GMR-beta peptide. Because the GMR-beta (A fwdarw C) clone is capable of forming functional high affinity receptors with transmembrane GMR-alpha (K-d = 64 pM), we feel that the cell surface retention of solGMR-alpha is independent of the GMR-beta mutation. We suggest that the co-expression and interaction of solGMR-alpha and GMR-beta represents a previously unrecognized GM-CSF receptor complex and a novel, ligand-independent mechanism of cytokine receptor assembly.

1/3,AB/3
 DIALOG(R)File 5:BIOSIS PREVIEWS(R)
 (c) 1998 BIOSIS. All rts. reserv.

11616531 BIOSIS Number: 98216531

In vitro characterization of the human recombinant soluble granulocyte-macrophage colony-stimulating factor receptor
 Brown C B; Beaudry P; Laing T D; Shoemaker S;
 Kaushansky K Room 2880, Health Sci. Cent., Univ. Calgary,
 3330 Hospital Dr. NW, Calgary, Alberta T2N 4N1, Canada
 Blood 85 (6). 1995. 1488-1495.

Full Journal Title: Blood

ISSN: 0006-4971

Language: ENGLISH

Print Number: Biological Abstracts Vol. 099 Iss. 010 Ref. 138707 We have cloned, expressed, and partially purified a naturally occurring, truncated, soluble form of the human granulocyte-macrophage-stimulating factor (GM-CSF) receptor alpha subunit to investigate its biochemical and biologic properties. The soluble receptor species lacks the transmembrane and cytoplasmic domains that are presumably removed from the intact receptor cDNA by a mechanism of alternative splicing. The resulting soluble 55- to 60-kD glycosylated receptor species binds GM-CSF with a dissociation constant (kd) of 3.8 nM. The soluble GM-CSF receptor successfully competes for %%%GM%%-%%%CSF%% binding not only with the %%%transmembrane%%-anchored %%%GM%%-%%%CSF%% receptor a subunit but also with the native oligomeric high-affinity receptor complex. In addition, in human bone marrow colony-forming assays, the soluble GM-CSF receptor species can antagonize the

activity of GM-CSF. Our data suggest that the soluble GM-CSF receptor may be capable of acting in vivo as a modulator of the biologic activity of GM-CSF.

1/3,AB/4
 DIALOG(R)File 5:BIOSIS PREVIEWS(R)
 (c) 1998 BIOSIS. All rts. reserv.

7312733 BIOSIS Number: 38093254

%%GM%%-%%%CSF%% RECEPTOR
 STRUCTURE AND %%%TRANSMEMBRANE%%
 SIGNALING DIPERSIO J F; GOLDE D W; GASSON J D
 11-640 FACTOR BUILDING, DIV. HEMATOL.-ONCOL.,
 DEP. MED., UCLA MED. CENTER, LOS ANGELES, CALIF.
 90024.

SYMPOSIUM ON BLOOD CELL GROWTH FACTORS:
 THEIR BIOLOGY AND CLINICAL APPLICATIONS HELD AT
 THE SECOND INTERNATIONAL CAPRI CONFERENCE,
 CAPRI, ITALY, OCTOBER 8-12, 1989. INT J CELL
 CLONING 8 (SUPPL. 1). 1990. 63-75. CODEN: IJCCE

Language: ENGLISH

Document Type: CONFERENCE PAPER

1/3,AB/5
 DIALOG(R)File 5:BIOSIS PREVIEWS(R)
 (c) 1998 BIOSIS. All rts. reserv.

7099816 BIOSIS Number: 88022561

EFFECTS OF RECOMBINANT HUMAN
 GRANULOCYTE-MACROPHAGE COLONY-STIMULATING
 FACTOR %%%GM%%-%%%CSF%%-R-H ON
 %%%TRANSMEMBRANE%% ELECTRICAL
 POTENTIALS IN GRANULOCYTES RELATIONSHIP
 BETWEEN ENHANCEMENT OF LIGAND-MEDIATED
 DEPOLARIZATION AND AUGMENTATION OF
 SUPEROXIDE ANION PRODUCTION SULLIVAN R;
 FREDETTE J P; LEAVITT J L; GADENNE A-S; GRIFFIN J
 D; SIMONS E R

HEMATOL. SECT., DEP. OF MED., BOSTON UNIV. MED.
 SCH., BOSTON, MASS. J CELL PHYSIOL 139 (2). 1989.
 361-369. CODEN: JCLLA

Full Journal Title: Journal of Cellular Physiology

Language: ENGLISH

When human granulocytes that have been primed with recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSFrh) are activated by ligands that stimulate the respiratory burst, the amount of superoxide anion (O2-) they generate is significantly increased. We have found that the accelerated rate of O2- release occurring under these conditions is accompanied by an antecedent increase in membrane depolarization. We examined the nature of the enhancement of membrane depolarization in GM-CSFrh-primed granulocytes and investigated its relationship to the increase in O2- generation by N-formyl methionyleucylphenylalanine (fMLP)-activated granulocytes. We found that augmented depolarization could not be accounted for by a change in the resting membrane potential induced by growth factor and was still present after either blocking passive transmembrane Na+ movement with dimethylamiloride or by increasing the membrane's permeability to K+ with valinomycin. When their ability to depolarize was virtually eliminated by dissipating the transmembrane K+ gradient, GM-CSFrh-pretreated cells continued to generate more O2- after fMLP than did control cells. These results indicate that augmentation of the granulocyte's ability to generate O2- anions, which is induced by priming with GM-CSFrh, is independent both of

the resting transmembrane potential and of alterations in the extent of membrane potential change induced by stimuli such as fMLP.

1/3,AB/6

DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

6188962 BIOSIS Number: 35054483

HUMAN %%%GM%%-%%%CSF%% RECEPTOR
BINDING AND %%%TRANSMEMBRANE%%
SIGNALLING

DIPERSIO J; BILLING P; KAUFMAN S; NACCACHE P;
BORGEAT P; GASSON J DIV. HEMATOL.-ONCOL., UCLA
SCH. MED., LOS ANGELES, CALIF. SYMPOSIUM ON
GROWTH FACTORS AND THEIR RECEPTORS: GENETIC
CONTROL AND RATIONAL APPLICATION HELD AT THE
17TH ANNUAL MEETING OF THE UCLA (UNIVERSITY OF
CALIFORNIA-LOS ANGELES) SYMPOSIA ON
MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE,
COLORADO, USA, JANUARY 24-30, 1988. J CELL
BIOCHEM SUPPL 0 (12 PART A). 1988. 90. CODEN:
JCBSD

Language: ENGLISH

Document Type: CONFERENCE PAPER

? s (gmcsf or gm())csf)

295 GMCSF

20946 GM

32963 CSF

7575 GM(W)CSF

S2 7744 (GMCSF OR GM())CSF)

? s s2 and fusion()protein

7744 S2

53154 FUSION

998884 PROTEIN

9339 FUSION(W)PROTEIN

S3 89 S2 AND FUSION()PROTEIN

? s s3 not (gmcsf or gm())csf()receptor

89 S3

295 GMCSF

20946 GM

32963 CSF

7575 GM(W)CSF

373966 RECEPTOR

306 (GMCSF OR GM(W)CSF)(W)RECEPTOR

S4 81 S3 NOT (GMCSF OR GM())CSF()RECEPTOR

? s s4 and membrane

81 S4

409735 MEMBRANE

S5 2 S4 AND MEMBRANE

? t s5/3,ab/1,2

5/3,AB/1

DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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13564242 BIOSIS Number: 99564242

The kinase domain of Jak2 mediates induction of Bcl-2 and
delays cell death in hematopoietic cells

Sakai I; Kraft A S

Div. Med. Oncol., Dep. Med., Univ. Colorado Health Sci.
Cent., Denver, CO 80262, USA

Journal of Biological Chemistry 272 (19). 1997.

12350-12358. Full Journal Title: Journal of Biological
Chemistry

ISSN: 0021-9258

Language: ENGLISH

Print Number: Biological Abstracts Vol. 104 Iss. 001 Ref.

005092 Granulocyte-macrophage colony-stimulating factor
(%%GM%%-%%%CSF%%), interleukin (IL)-3, and IL-5
stimulate DNA synthesis and proliferation and inhibit apoptosis
in hematopoietic cells. Multiple signal pathways are activated
by binding of these ligands to their receptors, which share a
common beta subunit. Janus protein kinase 2 (Jak2)
binds to the %%%membrane%% proximal domain of the
chain and is phosphorylated on receptor ligation. To explore
the role of Jak2 in the regulation of specific signal
transduction pathways, we constructed fusion proteins with a
CD 16 external domain, a CD7 transmembrane region, and a
Jak2 cytoplasmic domain. This cytoplasmic domain
consisted either of wild type Jak2 (CD16/Jak2-W) or Jak2
mutations with deletions of (a) the amino terminus
(CD16/Jak2-N), (b) kinase-like domain (CD16/Jak2-B), (c)
kinase domain (CD16/Jak2-C), or (d) amino-terminal and
kinase-like domains, leaving the kinase domain
(CD16/Jak2-K) intact. In contrast to the CD16/Jak2-W
%%fusion%% %%protein%%, which requires
crosslinking for activation, CD16/Jak2-N, CD16/Jak2-B,
and CD16/Jak2-K were constitutively phosphorylated,
and they stimulated Shc phosphorylation and increased
binding of STAT to DNA in Ba/F3 cells. Cell lines
derived from IL-3-dependent Ba/F3 cells stably
transfected with CD16/Jak2-W, CD16/Jak2-N, or
CD16/Jak2-B mammalian expression vectors died at a rate
similar to that of the parental cells on IL-3 deprivation. In
contrast, CD16/Jak2-K cell lines exhibited increased
expression of bcl-2 and pim-1 mRNA and maintained their
viability when compared with control cell lines. Thus, activation
of tyrosine phosphorylation by creating a CD16/Jak2-K fusion
is sufficient to activate pathways that prevent cell death.

5/3,AB/2

DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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9568860 BIOSIS Number: 94073860

GMP-140 P-SELECTIN-CD62 BINDS TO CHRONICALLY
STIMULATED BUT NOT RESTING CD4 POSITIVE T
LYMPHOCYTES AND REGULATES THEIR PRODUCTION
OF PROINFLAMMATORY CYTOKINES

DAMLE N K; KLUSSMAN K; DIETSCH M T;
MOHAGHEGHPOUR N; ARUFFO A BRISTOL-MYERS
SQUIBB PHARMCEUTICAL RES. INST., 3005 FIRST AVE.,
SEATTLE, WASH. 98121.

EUR J IMMUNOL 22 (7). 1992. 1789-1793. CODEN:
EJIMA

Full Journal Title: European Journal of Immunology

Language: ENGLISH

GMP-140 (P-selectin), a 140-kDa granular
%%membrane%% glycoprotein localized to the
.alpha.-granules of platelets and the Weibel-Palade bodies of
endothelial cells, is thought to play an important role in
adhesive interactions predominantly between granulocytes,
platelets and vascular endothelial cells during inflammation.
Although GMP-140 binds to granulocytes, its binding to
lymphocytes has not been demonstrated. Using genetically
engineered IgG C.gamma.1 %%fusion%%
%%protein%% of the extracellular domains of GMP-140,
we demonstrate that GMP-140 binds to chronically antigen
(Ag)-stimulated CD4+ T cells. Freshly isolated CD4+ T cells
did not bind GMP-140, but priming and subsequent
stimulation with alloantigen induced and gradually increased

expression of GMP-140-reactive structures on their surface. T cells isolated from rheumatoid synovial fluids also exhibited strong binding to GMP-140. The binding of GMP-140 to primed T cells is not influenced by preactivation with phorbol 12-myristate 13-acetate, is almost completely abolished by pretreatment of T cells with neuraminidase or trypsin, and is also strongly inhibited by EDTA, the soluble sulfated glycans dextran sulfate, fucoidan, and heparin, but not by chondroitin sulfates. In spite of its strong binding to Ag-primed T cells, GMP-140 did not modulate the proliferative responses of these cells to various stimuli. However, GMP-140 in conjunction with anti-T cell receptor .alpha..beta. monoclonal antibodies augmented the production of granulocyte-macrophage colony-stimulating factor %%%GM%%-%%%CSF%% and inhibited the production of interleukin-8 by Ag-primed T cells without influencing their tumor necrosis factor-.alpha. production. These results suggest that GMP-140 binds to chronically stimulated CD4+T cells and differentially modulates their production of proinflammatory cytokines. The ability of Ag-primed T cells to bind GMP-140 may facilitate interactions with activated platelets and endothelial cells affecting the course of inflammation.

? s (MAGE()3) AND (GMCSF OR GM()CSF)

261 MAGE
1672009 3
82 MAGE(W)3
295 GMCSF
20946 GM
32963 CSF
7575 GM(W)CSF

S6 4 (MAGE()3) AND (GMCSF OR GM()CSF)
? t s6/3,ab/all

6/3,AB/1
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

14068110 BIOSIS Number: 01068110
Transfer of tumor-associated antigen genes into dendritic cells for active immunotherapy of neoplastic diseases
Russo V; Sartirana C; Dalebra P; Rossini S; Traversari C; Bordignon C Ist. Sci. H.S. Raffaele, Milano, Italy
Blood 90 (10 SUPPL. 1 PART 1). 1997. 405A.
Full Journal Title: 39th Annual Meeting of the American Society of Hematology, San Diego, California, USA, December 5-9, 1997. Blood ISSN: 0006-4971
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 050 Iss. 002 Ref. 030518

6/3,AB/2
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

13814699 BIOSIS Number: 99814699
Transfection of IL-2 augments CTL response to human melanoma cells in vitro: Immunological characterization of a melanoma vaccine Van Elsas A; Aarnoudse C; Van Der Minne C E; Van Der Spek C W; Brouwenstijn A; Osanto S; Schrier P I
Dep. Clinical Oncol., Univ. Hosp., P.O. Box 9600, 2300 RC Leiden, Netherlands
Journal of Immunotherapy 20 (5). 1997. 343-353.
Full Journal Title: Journal of Immunotherapy
ISSN: *****

Language: ENGLISH

Print Number: Biological Abstracts Vol. 104 Iss. 012 Ref. 172303 We have transfected human melanoma cell line 518A2 with the cDNA encoding interleukin-2 (IL-2) or granulocyte-macrophage colony-stimulating factor (%%%GM%%-%%%CSF%%), and compared cytokine-producing clones for their ability to induce melanoma-specific cytotoxic T lymphocytes (CTL) from autologous peripheral blood mononuclear cells (PBMC) in vitro. The parental cell line expressed HLA-A1, HLA-A2, ICAM-1, LFA-3, in addition to the common CTL antigens MAGE-1, %%%MAGE%%-%%%3%%, tyrosinase, gp100, and Melan-A/MART-1. Stimulation of autologous PBMC responders with the IL-2-transfected clone 518/IL2.14 specifically induced CTL lines reactive with all cell lines derived from the autologous patient. Strikingly, %%%GM%%-%%%CSF%%-transfected 518A2 cells did not induce anti-tumor CTL reactivity. CTL induction against 518/ IL2.14 was independent of HLA class II expression or CD4 help. The parental cell line 518A2 gained immunogenic properties when high concentrations of IL-2 were supplied exogenously, indicating that IL-2 produced and present at high levels locally by itself enhanced immunogenicity. From the autologous CTL line reactive with 518/ IL2.14, clones were generated against an as yet unknown antigen, which was present in all autologous melanoma cell lines as well as in 7 of 15 HLA-A2+ melanoma cell lines tested, but not in melanocytes. These results will be discussed with respect to the possibility of using IL-2-transfected melanoma cells as a vaccine for treatment of patients with melanoma.

6/3,AB/3
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

13533636 BIOSIS Number: 99533636
Induction of peptide specific lymphocytes using peptide-pulsed cultured dendritic cells from patient with HLA-A2 and %%%MAGE%%-%%%3%% esophageal cancer cell line
Yamasaki S; Okino T; Li L; Kanaoka S; Shimada Y; Imamura M First Dep. Surgery, Kyoto Univ., Kyoto 606, Japan
Proceedings of the American Association for Cancer Research Annual Meeting 38 (0). 1997. 631.
Full Journal Title: Eighty-eighth Annual Meeting of the American Association for Cancer Research, San Diego, California, USA, April 12-16, 1997. Proceedings of the American Association for Cancer Research Annual Meeting ISSN: 0197-016X
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 006 Ref. 098416

6/3,AB/4
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

13249289 BIOSIS Number: 99249289
Induction of antigen-specific tumor immunity by genetic and cellular vaccines against MAGE: Enhanced tumor protection by coexpression of granulocyte-macrophage colony-stimulating factor and B7-1
Bueler H; Mulligan R C
Howard Hughes Medical Inst., Children's Hosp., Harvard Medical Sch., 300 Longwood Ave., Boston, MA 02115, USA
Molecular Medicine (Cambridge) 2 (5). 1996. 545-555.
Full Journal Title: Molecular Medicine (Cambridge)
ISSN: 1076-1551

Language: ENGLISH

Print Number: Biological Abstracts Vol. 102 Iss. 011 Ref. 164919 Background: A number of tumors express antigens that are recognized by specific cytotoxic T cells. The normal host immune responses, however, are not usually sufficient to cause tumor rejection. Using appropriate immunization strategies, tumor-specific antigens may serve as targets against which tumor-destructive immune responses can be generated. MAGE-1 and %%%MAGE%%-%%3%% are two clinically relevant antigens expressed in many human melanomas and other tumors, but not in normal tissues, except testis. Here, we have investigated whether DNA and cellular vaccines against MAGE-1 and %%%MAGE%%-%%3%% can induce antigen-specific anti-tumor immunity and cause rejection of MAGE-expressing tumors. Materials and Methods: Mice were immunized against MAGE-1 and %%%MAGE%%-%%3%% by subcutaneous injection of genetically modified embryonic fibroblasts or intramuscular injection of purified DNA. Mice were injected with lethal doses of B16 melanoma cells expressing the corresponding MAGE antigens or the unrelated protein SIV tat, and tumor development and survival were monitored. Results: Intramuscular expression of MAGE-1 and %%%MAGE%%-%%3%% by plasmid DNA injection and subcutaneous immunization with syngeneic mouse embryonic fibroblasts transduced with recombinant retroviruses to express these antigens induced specific immunity against tumors expressing MAGE-1 and %%%MAGE%%-%%3%%. Both CD4+ and CD8+ T cells were required for anti-tumor immunity. Coexpression of granulocyte-macrophage colony stimulating factor (%%GM%%-%%CSF%%) or B7-1 significantly increased anti-tumor immunity in an antigen-specific manner and resulted in a considerable proportion of mice surviving lethal tumor challenge. Conclusions: Our results suggest that genetic and cellular vaccines against MAGE and other tumor antigens may be useful for the therapy of tumors expressing specific markers, and that %%%GM%%-%%CSF%% and B7-1 are potent stimulators for the induction of antigen-specific tumor immunity.

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06aug98 16:29:08 User217743 Session D451.5

\$5.25 1.000 DialUnits File5

\$5.80 4 Type(s) in Format 3 (UDF)

\$11.60 8 Type(s) in Format 5 (UDF)

\$17.40 12 Types

\$22.65 Estimated cost File5

\$22.65 Estimated cost this search

\$32.05 Estimated total session cost 5.257 DialUnits

File 351:DERWENT WPI

1963-1998/UD=9830;UP=9827;UM=9825

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*File 351: All images are now present. The display formats have changed for 1998. See HELP FORM 351 for more information.

Set Items Description

? s (MAGE(3) AND (GMCSF OR GM()CSF)

50 MAGE

2761756 3

7 MAGE(W)3

11 GMCSF

3208 GM

1150 CSF

285 GM(W)CSF

S1 1 (MAGE(3) AND (GMCSF OR GM()CSF)
? t s1/29/

1/29/1

DIALOG(R)File 351:DERWENT WPI

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011742546

WPI Acc No: 98-159456/199814

XRAM Acc No: C98-051477

Treatment or prevention of melanoma - using melanoma cells expressing shared immuno-dominant antigen and modified for increased expression of a cytokine to improve immunogenicity
Patent Assignee: UNIV JOHNS HOPKINS SCHOOL
MEDICINE (UYJO); US DEPT HEALTH & HUMAN
SERVICES (USSH)

Inventor: ADLER A; JAFFEE E M; PARDOLL D M;

ROSENBERG S A; TOPALIAN S L Number of Countries: 077

Number of Patents: 002

Patent Family:

Patent No Kind Date Applicat No Kind Date Main IPC

Week WO-9806746 A2 19980219 97WO-US12868 A

19970804 C07K-014/00 199814 B AU-9738899 A

19980306 97AU-0038899 A 19970804 C07K-014/00

199830 E

Priority Applications (No Type Date): 96US-0024098 A

19960816 Patent Details:

Patent Kind Lan Pg Filing Notes Application Patent

WO-9806746 A2 E 27

Designated States (National): AL AM AT AU AZ BA BB BG
BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU
IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL
TJ TM TR TT UA UG UZ VN YU ZW

Designated States (Regional): AT BE CH DE DK EA ES FI
FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE
SZ UG ZW

AU-9738899 A Based on WO-9806746

Abstract (Basic): WO 9806746 A

Treatment or prevention of melanoma comprises (a) modifying a melanoma cell line (A) that expresses at least 1 shared immunodominant melanoma antigen (Ag) so that it produces increased levels of a cytokine (I) and (b) administering the modified cell to a mammal at risk of developing melanoma.

(A) are allogeneic and not MHC matched to the patient. Ag are melanocyte-specific differentiation or tumour-specific shared antigens, and particularly at least 3 Ag are expressed. Most preferably the cells express %%%MAGE%%-%%3%%, tyrosinase, MART-1/Melan-A, gp75 and gp100. Specified cell lines are 526-MEL and 624-MEL. Before administration, the cells are irradiated (typically at 10-30 kRad) and treated, by genetic manipulation to increase (I) production, or by formulating with non-specific adjuvants, to increase immunogenicity. Specifically (I) is granulocyte macrophage colony-stimulating factor (%%GM%%-%%CSF%%) and the gene encoding it is introduced using a conventional vector or as naked DNA, optionally under control of a melanocyte-specific or inducible promoter. Preferably the modified cells express over 36 ng (I)/million cells/day.

USE - The cells are administered by injection or inhalation, particularly subcutaneous or intradermal injection at 106-109 cells. They may be administered before, or in combination with, immunotherapy or other (e.g. surgical) methods of treatment.

ADVANTAGE - The modified cells provide a melanoma vaccine without requiring autologous or MHC (major

histocompatibility complex)-matched tumour cells. The use of shared antigens means that the vaccine will be effective in many different patients. Increasing the expression of (I) improves the immunogenicity of the cells. Since Ag are also expressed by some non-melanoma cancers (e.g. small cell lung cancer, colon and breast cancers), these may also be treated or prevented with the modified cells.

Dwg.0/0

Title Terms: TREAT; PREVENT; MELANOMA; MELANOMA; CELL; EXPRESS; SHARE; IMMUNO; DOMINANT; ANTIGEN; MODIFIED; INCREASE; EXPRESS; CYTOKINE; IMPROVE ; IMMUNOGENIC

Derwent Class: B04; D16

International Patent Class (Main): C07K-014/00

File Segment: CPI

Manual Codes (CPI/A-N): B04-F02; B14-S11C; D05-H07; D05-H08; D05-H09; D05-H10

Chemical Fragment Codes (M1):

01 M423 M781 M903 N135 P633 Q233 V288 V754
? b 34

06aug98 16:29:44 User217743 Session D451.6

\$9.75 1.000 DialUnits File351

\$3.35 1 Type(s) in Format 29

\$3.35 1 Types

\$13.10 Estimated cost File351

\$13.10 Estimated cost this search

\$45.15 Estimated total session cost 6.257 DialUnits

File 34:SciSearch(R) Cited Ref Sci 1990-1998/Jul W4

(c) 1998 Inst for Sci Info

Set Items Description

? s (MAGE()3) AND (GMCSF OR GM()CSF)

258 MAGE

1231183 3

96 MAGE(W)3

315 GMCSF

13908 GM

22925 CSF

7658 GM(W)CSF

S1 6 (MAGE()3) AND (GMCSF OR GM()CSF)

? t s1/3,ab/all

1/3,AB/1

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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06351537 Genuine Article#: YL383 Number of References:

191 Title: The molecular basis of cancer immunotherapy by cytotoxic T lymphocytes

Author(s): Lindauer M; Stanislawski T; Haussler A; Antunes E; Cellary A; Huber C; Theobald M (REPRINT)

Corporate Source: UNIV MAINZ,MED KLIN 3, DEPT HEMATOL, LANGENBECKSTR 1/D-55101

MAINZ//GERMANY/ (REPRINT); UNIV MAINZ,MED KLIN 3, DEPT HEMATOL/D-55101 MAINZ//GERMANY/

Journal: JOURNAL OF MOLECULAR MEDICINE-JMM, 1998, V76, N1 (JAN), P32-47 ISSN: 0946-2716 Publication date: 19980100

Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 Language: English Document Type: REVIEW

Abstract: The disappointing clinical results of cancer immunotherapy of the past few decades have not diminished the optimism about the potential of the new generation of immunotherapeutic strategies towards treatment of

malignant disease. Tremendous progress has been made over recent years in unveiling the molecular basis of antigen presentation and recognition by cytotoxic T lymphocytes (CTL). The molecular concepts that have emerged from these studies have led to the design of novel anticancer vaccines and CTL-based immunotherapeutics. This review is to highlight the current molecular insights of antigen presentation and CTL recognition/activation, and their impact on the rational design of therapeutic interventions that may result in protective, CTL-based antitumor immunity.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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06343636 Genuine Article#: YK969 Number of References:

39 Title: In vitro immunization and expansion of antigen-specific cytotoxic T lymphocytes for adoptive immunotherapy using peptide-pulsed dendritic cells

Author(s): Tsai V; Kawashima I; Keogh E; Daly K; Sette A; Celis E (REPRINT)

Corporate Source: CYTEL CORP,3525 JOHN HOPKINS COURT/SAN DIEGO//CA/92121 (REPRINT); CYTEL CORP,/SAN DIEGO//CA/92121; TAKARA SHUZO CO LTD,BIOTECHNOL RES LABS/OTSU/SHIGA 52021/JAPAN/ Journal: CRITICAL REVIEWS IN IMMUNOLOGY, 1998, V18, N1-2, P65-75 ISSN: 1040-8401 Publication date: 19980000 Publisher: BEGELL HOUSE INC, 79 MADISON AVE, SUITE 1205, NEW YORK, NY 10016-7892

Language: English Document Type: ARTICLE

Abstract: The design of an effective procedure to sensitize and expand antigen-specific cytotoxic T lymphocytes (CTL) in vitro is essential for the development of effective adoptive cellular immunotherapy protocols for cancer. We have analyzed the capacity of tissue culture-derived dendritic cells (DC) to present specific peptide epitopes to CTL precursors. Our results demonstrate that peptide-pulsed DC were efficient in generating CTL responses specific for various viral and tumor epitopes. Furthermore, IL-7 and IL-10 potentiated the ability of the peptide-pulsed DC to trigger antigen-specific CTL responses. The CTL generated using this procedure efficiently recognized the naturally processed antigens and could be expanded approximately 100- to 1000-fold in tissue culture in 10 to 15 days without a loss of activity and specificity. The results and procedures described herein may facilitate the development of effective CTL-based adoptive immunotherapy for chronic viral diseases and cancer.

1/3,AB/3

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

(c) 1998 Inst for Sci Info. All rts. reserv.

06162320 Genuine Article#: XY969 Number of References:

35 Title: Transfection of IL-2 augments CTL response to human melanoma cells in vitro: Immunological characterization of a melanoma vaccine Author(s): vanElsas A; Aarnoudse C; vanderMinne CE; vanderSpek CW; Brouwenstijn N; Osanto S; Schrier PI (REPRINT)

Corporate Source: UNIV LEIDEN HOSP,DEPT CLIN ONCOL, POB 9600/NL-2300 RC LEIDEN//NETHERLANDS/ (REPRINT); UNIV LEIDEN HOSP,DEPT CLIN ONCOL/NL-2300 RC LEIDEN//NETHERLANDS/ Journal: JOURNAL OF IMMUNOTHERAPY, 1997, V20, N5 (SEP), P343-353 ISSN: 1053-8550 Publication date: 19970900

Publisher: LIPPINCOTT-RAVEN PUBL, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106

Language: English Document Type: ARTICLE
 Abstract: We have transfected human melanoma cell line 518A2 with the cDNA encoding interleukin-2 (IL-2) or granulocyte-macrophage colony-stimulating factor (%%GM%%-%%CSF%%), and compared cytokine-producing clones for their ability to induce melanoma-specific cytotoxic T lymphocytes (CTL) from autologous peripheral blood mononuclear cells (PBMC) in vitro. The parental cell line expressed HLA-AI, HLA-A2, ICAM-1, LFA-S, in addition to the common CT, antigens MAGE-1, %%MAGE%%-%%3%%, tyrosinase, gp100, and Melan-A/MART-1. Stimulation of autologous PBMC responders with the IL-2-transfected clone 518/IL2.14 specifically induced CTL lines reactive with all cell lines derived from the autologous patient. Strikingly, %%GM%%-%%CSF%%-transfected 518A2 cells did not induce anti-tumor CTL reactivity. CTL induction against 518/IL2.14 was independent of HLA class II expression or CD4 help. The parental cell line 518A2 gained immunogenic properties when high concentrations of IL-2 were supplied exogenously, indicating that IL-2 produced and present at high levels locally by itself enhanced immunogenicity. From the autologous CTL line reactive with 518/IL2.14, clones were generated against an as yet unknown antigen, which was present in all autologous melanoma cell lines as well as in 7 of 15 HLA-A2(+) melanoma cell lines tested, but not in melanocytes. These results will be discussed with respect to the possibility of using IL-2-transfected melanoma cells as a vaccine for treatment of patients with melanoma.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
 (c) 1998 Inst for Sci Info. All rts. reserv.

06069304 Genuine Article#: BJ40F Number of References: 129 Title: Dendritic cell based therapy of cancer Author(s): Lotze MT (REPRINT) ; Shurin M; Davis I; Amoscato A; Storkus WJ Corporate Source: UNIV PITTSBURGH,DEPT SURG, SCH MED, 300 KAUFMANN BLDG, 3471 5TH AVE/PITTSBURGH/PA/15213 (REPRINT) , 1997, V417, P551-569 ISSN: 0065-2598 Publication date: 19970000 Publisher: PLENUM PRESS DIV PLENUM PUBLISHING CORP, 233 SPRING ST, NEW YORK, NY 10013ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY Series: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY Language: English Document Type: REVIEW

1/3,AB/5

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
 (c) 1998 Inst for Sci Info. All rts. reserv.

06051505 Genuine Article#: XR802 Number of References: 58 Title: Functional heterogeneity of HLA-A*02 subtypes revealed by presentation of a %%MAGE%%-%%3%%-encoded peptide to cytotoxic T cell clones Author(s): Fleischhauer K (REPRINT) ; Tanzarella S; Russo V; Sensi ML; vanderBruggen P; Bordinon C; Traversari C Corporate Source: SAN RAFFAELE SCI INST,DIBIT, TELETHON INST GENE THERAPY, VIA OLGETTINA 58/I-20132 MILAN//ITALY/ (REPRINT); SAN RAFFAELE SCI INST,GENE THERAPY PROGRAM/I-20132 MILAN//ITALY/; LUDWIG INST CANC RES,BRUSSELS//BELGIUM/; IST NAZL TUMORI,I-20133 MILAN//ITALY/ Journal: JOURNAL

OF IMMUNOLOGY, 1997, V159, N5 (SEP 1), P2513-2521 ISSN: 0022-1767 Publication date: 19970901 Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 Language: English Document Type: ARTICLE Abstract: The peptide-binding and presentation characteristics of seven naturally occurring HLG-A2 subtypes were studied using M3(271), a peptide derived from the tumor-specific Ag encoded by gene %%MAGE%%-%%3%%, which has been shown to be processed and presented by A*0201(+) melanoma lines. Three independent M3(271)-specific CTL clones were obtained from two unrelated A*0201(+) donors. B lymphoblastoid cell lines (BLCLs) expressing A*0201, A*0207, or A*0209 could be sensitized to lysis by all three clones upon incubation with the relevant peptide. Furthermore, the same BLCLs were able to present endogenous M3(271) in IFN-gamma release assays. These findings demonstrate, for the first time, the existence of a functional overlap between A*0207 and other A*02 subtypes. One of the CTL clones also lysed M3(271)-pulsed BLCLs expressing A*0204 and A*0206, while the other two clones recognized M3(271) only in the context of either of these two subtypes. Peptide-pulsed BLCLs expressing A*0202 or A*0205 were not lysed, although A*0205 and, with lower affinity, A*0202 molecules were shown to bind peptide M3(271). These findings have implications for the selection of cancer patients for specific immunotherapy with peptide M3(271).

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05257476 Genuine Article#: VL189 Number of References: 57 Title: INDUCTION OF ANTIGEN-SPECIFIC TUMOR-IMMUNITY BY GENETIC AND CELLULAR VACCINES AGAINST MAGE - ENHANCED TUMOR PROTECTION BY COEXPRESSION OF GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR AND B7-1 Author(s): BUELER H; MULLIGAN RC Corporate Source: CHILDRENS HOSP,HOWARD HUGHES MED INST,300 LONGWOOD AVE/BOSTON//MA/02115; CHILDRENS HOSP,HOWARD HUGHES MED INST/BOSTON//MA/02115; HARVARD UNIV,SCH MED,DEPT GENET/BOSTON//MA/02115 Journal: MOLECULAR MEDICINE, 1996, V2, N5 (SEP), P545-555 ISSN: 1076-1551

Language: ENGLISH Document Type: ARTICLE Abstract: Background: A number of tumors express antigens that are recognized by specific cytotoxic T cells. The normal host immune responses, however, are not usually sufficient to cause tumor rejection. Using appropriate immunization strategies, tumor-specific antigens may serve as targets against which tumor-destructive immune responses can be generated. MAGE-1 and %%MAGE%%-%%3%% are two clinically relevant antigens expressed in many human melanomas and other tumors, but not in normal tissues, except testis. Here, we have investigated whether DNA and cellular vaccines against MAGE-1 and %%MAGE%%-%%3%% can induce antigen-specific anti-tumor immunity and cause rejection of MAGE-expressing tumors.

Materials and Methods: Mice were immunized against MAGE-1 and %%MAGE%%-%%3%% by subcutaneous injection of genetically modified embryonic fibroblasts or intramuscular injection of purified DNA. Mice were injected with lethal doses of B16 melanoma cells

expressing the corresponding MAGE antigens or the unrelated protein SIV tat, and tumor development and survival were monitored.

Results: Intramuscular expression of MAGE-1 and %%%MAGE%%-%%%3%%% by plasmid DNA injection and subcutaneous immunization with syngeneic mouse embryonic fibroblasts transduced with recombinant retroviruses to express these antigens induced specific immunity against tumors expressing MAGE-1 and %%%MAGE%%-%%%3%%%. Both CD4(+) and CD8(+) T cells were required for anti-tumor immunity. Coexpression of granulocyte-macrophage colony-stimulating factor (GM-CSF) or B7-1 significantly increased anti-tumor immunity in an antigen-specific manner and resulted in a considerable proportion of mice surviving lethal tumor challenge.

Conclusions: Our results suggest that genetic and cellular vaccines against MAGE and other tumor antigens may be useful for the therapy of tumors expressing specific markers, and that %%%GM%%-%%%CSF%%% and B7-1 are potent stimulators for the induction of antigen-specific tumor immunity.

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\$2.50 1 Type(s) in Format 4 (UDF)

\$10.00 4 Type(s) in Format 5 (UDF)

\$15.00 6 Types

\$19.25 Estimated cost File34

\$19.25 Estimated cost this search

\$64.40 Estimated total session cost 7.257 DialUnits

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